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(12) # PATENT APPLICATION A1

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(56) **List of Documents Cited in the Search Report:**
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(60) **Reference(s) to Other Related Domestic Documents:**

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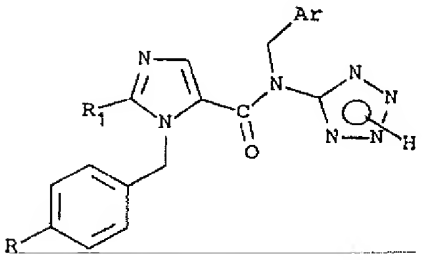
(54) **Imidazole-5-carboxamide compounds, their process of preparation, their intermediates and their use in therapeutics.**

(57) The present invention relates to the imidazolecarboxamides of formula:



in which the R, R1 and Ar groups are defined as indicated in the description. The invention also relates to their process of preparation and their application in therapeutics as antagonist agents for angiotensin II, useful in the treatment of hypertension, circulatory disorders and glaucoma.

FR 2 707 641-A1

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FIELD OF THE INVENTION:

The present invention relates to novel imidazole-5-carboxamide compounds, their process of preparation and their use in therapeutics as active ingredients useful in the treatment of hypertension, circulatory disorders and glaucoma.

PRIOR ART:

A certain number of imidazole anglotensin II antagonist derivatives usable as antihypertensive agents are already known in the literature. Applications EP-A-253 310 and EP-A-324 377 describe imidazole derivatives comprising numerous substituent possibilities, including an unsaturated chain or acid derivatives in Position 5 of the imidazole ring. Patent applications EP-A-403 158, EP-A-403 159, EP-A-425 211, EP-A-535 463, EP-A-535 465 and DE-A-4132632 also describe imidazolyl-alkenoic acids with an unsaturated chain in Position 5 of the imidazole ring; application WO-A-91/00277 describes substituted imidazoles with an aldehyde function in Position 5 of the imidazole ring. Application EP-A-427 463 describes substituted N-(imidazolyl) alkyl alanine derivatives with an amino acid residue in Position 5 of the imidazole ring. Application EP-A-437 103 describes imidazole-5-(alkyl)carboxamide derivatives substituted by carbon chains. Application EP-A-503 785 describes derivatives of 1-(biphenyl-methyl)-imidazole-5-carboxylic acid substituted in position 4 of the imidazole ring. Application JP-A-89 113 372 describes derivatives of imidazole-5-carboxamide with fungicide properties.

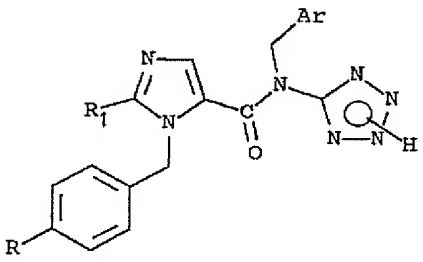
GOAL OF THE INVENTION:

None of these prior documents describes or suggests derivatives of imidazole-5-carboxamide whose amide function is substituted on nitrogen by a tetrazolyl group. It turns out that such derivatives demonstrate excellent angiotensin II antagonist activity. Thus, the present invention proposes derivatives of imidazole-5-carboxamide with a tetrazolyl group as the substituent for the amide function.

OBJECT OF THE INVENTION:

The compounds of the invention are characterized in that they are chosen from among the group comprised of:

(i) imidazole-5-carboxamides of formula:



(I)

in which:

- R_1 represents an n-propyl or n-butyl group,
- R represents:
  - * a CO_2R_2 group in which R_2 represents:
    - the hydrogen atom,
    - a C_1-C_5 linear or branched alkyl group,
    - a benzyl group,

- a group of formula –CHR_3-O-CO-R_4 in which R_3 represents a hydrogen atom or a methyl group and R_4 represents a C_1-C_5 linear or branched alkyl group, a C_2-C_6 linear or branched alkoxy group or a C_5-C_6 cycloalkyloxy group.

* a 2-chloro-phenyl-sulfonylamino-carbonyl group, or

* a tetrazol-5-yl-amino-carbonyl group,

- Ar represents:

* A phenyl group optionally substituted by one or more of the following atoms or groups: methyl, 1-methyl-ethyl, phenyl, chloro, cyano, methoxy, benzyloxy, trifluoromethyloxy, trifluoromethyl, N,N-dimethyl-amino, carboxyl, methylcarbonyl,

* A 3,4-methylenedioxyphenyl group,

* A 3-furanyl group,

* A 2-thienyl group, or

* A 2-naphtyl group; and

(ii) their addition salts with mineral or organic bases.

The invention also relates to the use in therapeutics of these compounds and their process of preparation.

DETAILED DESCRIPTION OF THE INVENTION:

C_1-C_5 linear or branched alkyl group here is understood to refer to an alkyl group with a linear or branched hydrocarbon chain comprising up to 5 carbon atoms. C_2-C_6 linear or branched alkoxy group here is understood to refer to an alkoxy group whose hydrocarbon chain is linear or branched and comprises 2 to 6 carbon atoms.

C_5-C_6 cycloalkyloxy group here is understood to refer to a cyclopentyloxy, cyclopentylmethoxy or cyclohexyloxy group.

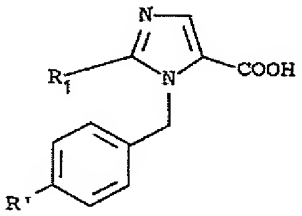
From the addition salts with mineral and organic bases, addition salts formed with sodium hydroxide, potassium hydroxide, magnesium hydroxide, calcium hydroxide, lithium hydroxide, lysine, cysteine, arginine, monoethanolamine, meglumine, betaine, diethylamine and dicyclohexylamine will be preferred.

The preferred compounds of the invention are the compounds of formula I in which:

- R_1 represents an n-butyl group,
- R represents a carboxyl group, a methoxycarbonyl group or a 1-(cyclohexyloxycarbonyloxy)ethoxycarbonyl group,
- Ar represents a 2-thienyl group, a 3-furanyl group or a phenyl group optionally substituted by a chlorine atom, a methyl group, a methoxy group, or a 3,4-methylenedioxy group, as well as the corresponding salts obtained by reaction with an organic or mineral base.

The compounds of formula I according to the invention may be prepared according to a process characterized in that:

a) a compound of formula:

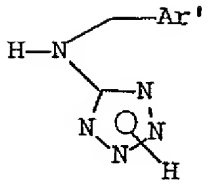


(II)

is caused to react, in which

- R_1 represents an n-propyl or n-butyl group,
- R' represents a $CO_2R'_2$ group in which R'_2 represents
  - A C_1-C_5 linear or branched alkyl group,
  - A benzyl group,
  - A group of formula $-CHR_3-O-CO-R_4$ in which R_3 represents a hydrogen atom or a methyl group and R_4 represents a C_1-C_5 linear or branched alkyl group, a C_2-C_6 linear or branched alkoxy group, or a C_5-C_6 cycloalkyloxy group,

with a compound of formula:

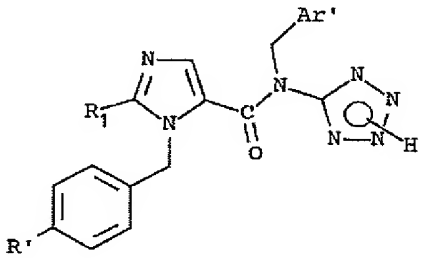


(III)

in which Ar' represents:

* a phenyl group optionally substituted by one or more of the following atoms or groups: methyl, 1-methyl-ethyl, phenyl, chloro, cyano, methoxy, benzyloxy, trifluoromethyloxy, trifluoromethyl, N,N-dimethylamino or methoxycarbonyl,
* a 3,4-methylenedioxy-phenyl group,
* a 3-furanyl group,
* a 2-thienyl group, or
* a 2-naphtyl group,

to form an amide bond, according to a method known in itself, in an organic solvent, such as for example tetrahydrofurane or dimethylformamide, and in the presence of a catalyst of a known type to form peptide bonds, such as for example 1,1'-carbonyl-diimidazole (C.D.I.) or N,N'-dicyclohexylcarbodiimide (D.C.C.), at a temperature between ambient temperature (15-25°C) and the reflux temperature of the reaction medium under atmospheric pressure for 0.5 to 24 hours and to obtain a compound of formula:



(I')

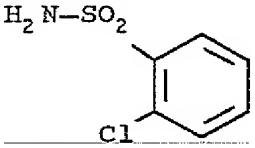
in which R_1, R' and Ar' have the same meanings as above; and

b) if necessary, the compounds of formula I' thus obtained are subjected to the following treatments:

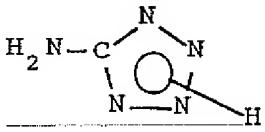
(i) saponifying a compound of formula I' in which at least one of the R' and Ar' groups represents or contains an alkoxycarbonyl group, according to a method known in itself, particularly in the presence of a strong base such as for example an aqueous sodium or potassium hydroxide, in dimethoxyethane or an alcohol such as for example methanol, to obtain a compound of formula I in which at least one of the R and Ar groups represents or contains a COOH group, or

(ii) deprotecting a compound of formula I' in which R' represents a benzyloxycarbonyl group according to methods known to the person skilled in the art, particularly by catalytic hydrogenation in the presence of a catalyst such as palladized charcoal, to obtain a compound of formula I in which R represents a COOH group;

(iii) acylating an arylsulfonamide of formula:



or 5-amino-tetrazol of formula:



by a monoacid of formula I obtained according to one of the previous steps (i) and (ii), in which R represents a COOH group and Ar has the same meanings as above for Ar' in formula III, according to a method known in itself, particularly in the presence of a coupling reagent such as for example N,N-dicyclohexylcarbodiimide or 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride, to obtain a compound of formula I in which R_1 and Ar have the same meanings as above and R represents a 2-chlorophenylsulfonylaminocarbonyl group or a (tetrazol-5-yl)-aminocarbonyl group.

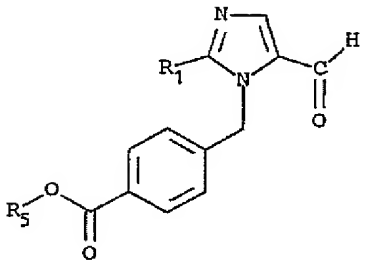
In a variation, one may also obtain the compounds of formula I' above according to a process characterized in that:

(i) a compound of formula II is caused to react with a halogenating agent such as for example thionyl chloride to obtain the corresponding acid chloride, then

(ii) said acid chloride is caused to react with a compound of formula III, in the presence of a mineral base such as for example sodium hydrogencarbonate, or an organic base, such as for example pyridine, to obtain a compound of formula I' such as described above.

To access the compounds of formula II, the following process is recommended:

one oxidizes a compound of formula:



(IV)

in which R_1 represents an n-propyl or n-butyl group and R_5 represents a C_1-C_5 linear or branched alkyl group, a benzyl group or a group of formula $-CHR_3$-O-CO-R_4 in which R_3 and R_4 have the same meanings as above in formula I, according to processes known to the person skilled in the art, such as for example by reaction with sodium chlorite, in the presence of a solvent such as a mixture of 1,1-dimethylethanol and water buffered with monosodium phosphate to obtain a compound of formula II in which R_1 represents an n-propyl or n-butyl group and R' represents a $CO_2R'_2$ group in which R'_2 represents a C_1-C_5 alkyl group, a benzyl group or a group of formula -CHR_3 -O-CO-R_4 in which R_3 and R_4 have the same meanings as above. The imidazole-5-carboxylic acids of formula II in which R_1 represents an n-propyl or n-butyl group and R' represents an ethoxycarbonyl group, a pentyloxycarbonyl group, a benzyloxycarbonyl group or a group of formula -CO_2-CHR_3 -O-CO-R_4 in which R_3 and R_4 have the same meanings as above, are novel and constitute one of the objects of the invention.

The imidazoles-carboxaldehydes of formula IV in which R_1 represents an n-propyl or n-butyl group and R_5 represents a group of formula $-CHR_3-O-CO-R_4$ in which R_3 and R_4 have the same meanings as above, are prepared by reaction of a compound of formula IV in which R_1 has the same meanings as above and R_5 represents a hydrogen atom, with a halogen derivative of formula:

$$Cl-CHR_3-O-CO-R_4 \qquad (V)$$

in which R_3 and R_4 have the same meanings as above, in the presence of an alkaline agent, such as for example potassium carbonate or sodium hydride in the presence of a solvent.

To access the compounds of formula III, the following process is recommended:

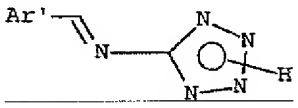
(i) one causes to react an aldehyde of formula:

$$Ar'-CHO$$

in which Ar' represents:

* a phenyl group optionally substituted by one or more of the following atoms or groups: methyl, 1-methylethyl, phenyl, chloro, cyano, methoxy, benzyloxy, trifluoromethyloxy, trifluoromethyl, N,N-dimethylamino, methoxycarbonyl,
* a 3,4-(methylenedioxy)phenyl group,
* a 3-furanyl group,
* a 2-thienyl group, or
* a 2-naphtyl group,

with 5-amino-tetrazol to form an arylimine of formula:



in which Ar' has the same meanings as above;

(ii) the arylamine thus obtained is reduced according to a method known in itself such as for example with hydrogen in the presence of a catalyst, or with sodium borohydride, in a solvent such as for example methanol to obtain a compound of formula III in which Ar' has the same meanings as above.

The amino tetrazols of formula III in which Ar' represents:

* a phenyl group substituted by one of the following groups: 4-methoxy, 3,4-dichloro, 4-trifluoromethyl, 4-cyano, 4-dimethylamino, 4-benzyloxy, 4-(1-methylethyl), 4-phenyl, 3,4-methylenedioxy and 4-trifluoromethyloxy,
* a 2-thienyl group,
* a 3-furanyl group, or
* a 2-naphtyl group,

are novel and constitute one of the objects of the invention. They are involved as synthesis intermediates in obtaining compounds of formula I according to the invention.

The invention will be better understood upon reading the following examples of preparation in which the term "preparation" refers to obtaining any intermediate product and the term "example" refers to obtaining any product of formula I according to the invention. These elements are intended to illustrate the invention but should not limit its scope.

PREPARATION 1

4-[(2-butyl-5-formyl-1H-imidazole-1-yl)-methyl]benzoic, 1-cyclohexyloxycarbonyloxy)ethyl ester acid

To a solution of 5.54 g (0.019 mole) of 4-[(2-butyl-5-formyl-1H-imidazole-1-yl)-methyl]benzoic acid in 25 ml of anhydrous N,N-dimethylformamide (DMF), cooled to 0°C, under nitrogen atmosphere, is added 0.63 g (0.021 mole) of sodium hydride in 80% suspension in mineral oil. This is agitated at 0°C for 20 minutes then a solution of 4 g (0.019 mole) carbonic acid, 1-chloroethyl cyclohexyl ester (diester compound of formula V where R_3 is 1-chloroethyl and R_4 is cyclohexyloxy), in 5 ml of DMF, then 0.1 g (6.6×10^{-4} mole) of sodium iodide is added dropwise. The reaction mixture is then agitated at 90°C for 21 hours. After cooling to 0°C, 150 ml of water is added. The aqueous

phase is acidified up to pH = 6.5 with 1N hydrochloric acid and extracted by ethyl acetate. The organic phase is washed with water, dried by magnesium sulfate, filtered and concentrated under reduced pressure. The residue obtained is purified by silica chromatography by elution with a 90/10 then 40/10 toluene/ethyl acetate mixture (V/V). 5.35 g of a yellow oil is obtained (yield = 61%).

NMR ^1H (300 MHz; $CDCl_3$; ppm)

0.79(t, 3H); 1.19-1.63 (m, 12H); 1.61(d, 3H); 1.82 (m, 2H); 2.63(t, 2H); 4.54 (m, 1H); 5.67 (s, 2H); 6.85 (q, 1H); 7.18 (d, 2H); 7.93 (d, 2H); 7.94 (s, 1H); 9.64 (s, 1H).

PREPARATION 2

2-butyl-1-[(4-methoxycarbonyl-phenyl)methyl]-1H-imidazole-5-carboxylic acid

To a solution of 10 g (0.0333 mole) of 4-[2-butyl-5-formyl-1H-imidazole-1-yl)methyl]benzoic, methyl ester acid, in a mixture of 400 ml of tetrahydrofurane (THF), 400 ml of 1,1-dimethylethanol and 170 ml of a 2 M solution of 2-methyl-2-butene in THF, is added a solution of 30 g (0.333 mole) of sodium chlorite and 30 g (0.217 mole) of monohydrated sodium dihydrogen phosphate in 330 ml of water. The reaction mixture is agitated at ambient temperature for 20 hours. The solvent volume is reduced by ¾ by evaporation under reduced pressure. The solid precipitate is filtered, washed thoroughly in water and dried under vacuum. 9.72 g of a white solid is obtained (yield = 92%).
M PT. = 212°C.

The following preparation products can be obtained by an operation similar to that of Preparation 2:

PREPARATION 3

2-butyl-1-[(4-ethoxycarbonyl-phenyl)methyl]-1H-imidazole-5-carboxylic acid
M PT. = 202°C

PREPARATION 4

2-butyl-1-[(4-pentyloxycarbonyl-phenyl)methyl]-1H-imidazole-5-carboxylic acid

M PT. = 168°C

PREPARATION 5

2-butyl-1-[(4-phenylmethoxycarbonyl-phenyl)methyl]-1H-imidazole-5-carboxylic acid

M PT. = 170°C

PREPARATION 6

2-butyl-1-[(4-((1-(cyclohexyloxycarbonyloxy)ethyl)oxycarbonyl)phenyl)methyl]-1H-imidazole-5-carboxylic acid

M PT. = 50°C

PREPARATION 7

1-[(4-methoxycarbonyl-phenyl)methyl]-2-propyl-1H-imidazole-5-carboxylic acid

M PT. = 225°C

PREPARATION 8

N-(thien-2-yl-methyl)-1H-tetrazol-5-amine

To a suspension of 2.12 g (0.025 mole) of 5-amino-2H-tetrazol in 30 ml of anhydrous methanol is added, under nitrogen atmosphere, 10 g of molecular sieve (0.3 nm), 2.52 g (0.025 mole) of trimethylamine and 2.8 g (0.025 mole) of thiophene-2-carboxaldehyde. The reaction mixture is heated to reflux for 3.5 hours then cooled to 0°C. Then 3 g (0.079 mole) of $NaBH_4$ is added by fractions and left to agitate for 3 hours at 0°C. The methanol is then evaporated under reduced pressure. The residue is diluted with 50 ml of water and filtered. The filtrate is washed with ether (2 x 25 ml) and acidified up to pH = 3 by concentrated hydrochloric acid. The precipitate formed is filtered, washed in water and dried under vacuum. Thus 1.9 g of a white solid is obtained (yield = 45%).

M PT. = 210°C

The following products are obtained by an operation similar to that of Preparation 8:

PREPARATION 9

N-(furan-3-yl-methyl)-1H-5-amine
M PT. = 186°C

PREPARATION 10

N-((4-methyoxyphenyl)methyl)-1H-tetrazol-5-amine
M PT. = 230°C

PREPARATION 11

N-((3-chlorophenyl)methyl)-1H-tetrazol-5-amine
M PT. = 208°C

PREPARATION 12

N-(napht-2-yl-methyl)-1H-tetrazol-5-amine
M PT. = 234°C

PREPARATION 13

N-((3,4-dichlorophenyl)methyl)-1H-tetrazol-5-amine
M PT. = 220°C

PREPARATION 14

N-((4-trifluoromethylphenyl)methyl)-1H-tetrazol-5-amine
M PT. = 226°C

PREPARATION 15

N-((4-cyanophenyl)methyl)-1H-tetrazol-5-amine
M PT. = 230°C

PREPARATION 16

N-((4-dimethylamino-phenyl)methyl)-1H-tetrazol-5-amine
M PT. = 213°C

PREPARATION 17

N-((4-phenylmethoxy-phenyl)methyl)-1H-tetrazol-5-amine
M PT. = 223°C

PREPARATION 18

N-((4-(1-methylethyl)phenyl)methyl)-1H-tetrazol-5-amine
M PT. = 205°C

PREPARATION 19

N-((biphenyl-4-yl)methyl)-1H-tetrazol-5-amine
M PT. = 260°C

PREPARATION 20

N-((3,4-methylenedioxyphenyl)methyl)-1H-tetrazol-5-amine
M PT. = 220°C

PREPARATION 21

N-((4-trifluoromethyloxy-phenyl)methyl)-1H-tetrazol-5-amine
M PT. = 224°C

EXAMPLE 1

2-butyl-1-[(4-(methyoxycarbonyl)phenyl)methyl]-N-[(thien-2-yl)methyl]-N-[-1H-tetrazol-5-yl]-1H-imidazole-5-carboxamide

To a suspension of 3.89 g (0.0123 mole) of 2-butyl-1-[(4-(methoxycarbonyl)phenyl)methyl]-1H-imidazole-5-carboxylic acid in 190 ml of anhydrous tetrahydrofurane, is added, under nitrogen atmosphere, 2.19 g (0.0135 mole) of 1,1'-carbonyldiimidazole. The reaction mixture is brought to reflux for 3 hours then 2.45 g (0.0135 mole) of N-(thien-2-yl-methyl)-tetrazol-5-amine is added. The reaction mixture is then maintained at reflux for 3 hours, and then concentrated under reduced pressure. The residue is taken up with 100 ml of water and acidified at pH = 4 with 1N hydrochloric acid. The precipitate obtained is filtered, rinsed in water and dried under vacuum. After recrystallization in ethyl acetate, 3.22 g of a white solid in fine crystals is obtained (yield = 55%).

M PT. = 190°C

The following examples of products can be obtained by an operation similar to that of Example 1:

EXAMPLE 2:

1-[(4-(methoxycarbonyl)phenyl)methyl]-2-propyl-N-[(thien-2-yl)methyl]-N-[-1H-tetrazol-5-yl]-1H-imidazole-5-carboxamide

M PT. = 191°C

EXAMPLE 3:

2-butyl-1-[(4-(methoxycarbonyl)phenyl)methyl]-N-[-1H-tetrazol-5-yl]-1H-imidazole-5-carboxamide

M PT. = 190°C

EXAMPLE 4:

2-butyl-1-[(4-(methoxycarbonyl)phenyl)methyl]-N-[(furan-3-yl)methyl]-N-[-1H-tetrazol-5-yl]-1H-imidazole-5-carboxamide

M PT. = 200°C

EXAMPLE 5:

2-butyl-1-[(4-(methoxycarbonyl)phenyl)methyl]-N-[(4-methoxyphenyl)methyl]-N-[-1H-tetrazol-5-yl]-1H-imidazole-5-carboxamide
M PT. = 209 °C

EXAMPLE 6:

2-butyl-1-[(4-(methoxycarbonyl)phenyl)methyl]-N-[(2-chlorophenyl)methyl]-N-[-1H-tetrazol-5-yl]-1H-imidazole-5-carboxamide
M PT. = 151 °C

EXAMPLE 7:

2-butyl-1-[(4-(methoxycarbonyl)phenyl)methyl]-N-[(3-chlorophenyl)methyl]-N-[-1H-tetrazol-5-yl]-1H-imidazole-5-carboxamide
M PT. = 192 °C

EXAMPLE 8:

2-butyl-1-[(4-(methoxycarbonyl)phenyl)methyl]-N-[(4-chlorophenyl)methyl]-N-[-1H-tetrazol-5-yl]-1H-imidazole-5-carboxamide
M PT. = 204 °C

EXAMPLE 9:

2-butyl-1-[(4-(methoxycarbonyl)phenyl)methyl]-N-[(4-methylphenyl)methyl]-N-[-1H-tetrazol-5-yl]-1H-imidazole-5-carboxamide
M PT. = 194 °C

EXAMPLE 10:

2-butyl-1-[(4-(methoxycarbonyl)phenyl)methyl]-N-[(napht-2-yl)methyl]-N-[-1H-tetrazol-5-yl]-1H-imidazole-5-carboxamide
M PT. = 206 °C

EXAMPLE 11:

2-butyl-1-[(4-(methoxycarbonyl)phenyl)methyl]-N-[(3,4-dichlorophenyl)methyl]-N-[-1H-tetrazol-5-yl]-1H-imidazole-5-carboxamide

M PT. = 213 °C

EXAMPLE 12:

2-butyl-1-[(4-(methoxycarbonyl)phenyl)methyl]-N-[(4-trifluoromethyl-phenyl)methyl]-N-[-1H-tetrazol-5-yl]-1H-imidazole-5-carboxamide

M PT. = 192 °C

EXAMPLE 13:

2-butyl-1-[(4-(methoxycarbonyl)phenyl)methyl]-N-[(4-(N,N-dimethylamino)-phenyl)methyl]-N-[-1H-tetrazol-5-yl]-1H-imidazole-5-carboxamide

M PT. = 170 °C

EXAMPLE 14:

2-butyl-1-[(4-(methoxycarbonyl)phenyl)methyl]-N-[(4-(phenylmethoxy)phenyl)-methyl]-N-[-1H-tetrazol-5-yl]-1H-imidazole-5-carboxamide

M PT. = 202 °C

EXAMPLE 15:

2-butyl-1-[(4-(methoxycarbonyl)phenyl)methyl]-N-[(4-cyanophenyl)methyl]-N-[-1H-tetrazol-5-yl]-1H-imidazole-5-carboxamide

M PT. = 220 °C

EXAMPLE 16:

2-butyl-1-[(4-(methoxycarbonyl)phenyl)methyl]-N-[(4-(1-methylethyl)phenyl)methyl]-N-[-1H-tetrazol-5-yl]-1H-imidazole-5-carboxamide

M PT. = 187 °C

EXAMPLE 17:

2-butyl-1-[(4-(methoxycarbonyl)phenyl)methyl]-N-[biphenyl-4-yl-methyl]-N-[-1H-tetrazol-5-yl]-1H-imidazole-5-carboxamide
M PT. = 170 °C

EXAMPLE 18:

2-butyl-1-[(4-(methoxycarbonyl)phenyl)methyl]-N-[(4-methoxycarbonyl)phenyl)-methyl]-N-[-1H-tetrazol-5-yl]-1H-imidazole-5-carboxamide
M PT. = 200 °C

EXAMPLE 19:

2-butyl-1-[(4-(methoxycarbonyl)phenyl)methyl]-N-[(4-(trifluoromethyloxy)phenyl)-methyl]-N-[-1H-tetrazol-5-yl]-1H-imidazole-5-carboxamide
M PT. = 191 °C

EXAMPLE 20:

2-butyl-1-[(4-(methoxycarbonyl)phenyl)methyl]-N-[(3,4-methylenedioxyphenyl)-methyl]-N-[-1H-tetrazol-5-yl]-1H-imidazole-5-carboxamide
M PT. = 210 °C

EXAMPLE 21:

2-butyl-1-[(4-(ethoxycarbonyl)phenyl)methyl]-N-[(thien-2-yl)methyl]-N-[-1H-tetrazol-5-yl]-1H-imidazole-5-carboxamide
M PT. = 165 °C

EXAMPLE 22:

2-butyl-1-[(4-(ethoxycarbonyl)phenyl)methyl]-N-[phenylmethyl]-N-[1H-tetrazol-5-yl]-1H-imidazole-5-carboxamide
M PT. = 184 °C

EXAMPLE 23:

2-butyl-1-[(4-(pentyloxycarbonyl)phenyl)methyl]-N-[phenylmethyl]-N-[1H-tetrazol-5-yl]-1H-imidazole-5-carboxamide
M PT. = 181 °C

EXAMPLE 24:

2-butyl-1-[(4-(pentyloxycarbonyl)phenyl)methyl]-N-[(4-chlorophenyl)methyl]-N-[1H-tetrazol-5-yl]-1H-imidazole-5-carboxamide
M PT. = 191 °C

EXAMPLE 25:

2-butyl-1-[(4-(phenylmethoxycarbonyl)phenyl)methyl]-N-[(3,4-methylenedioxyphenyl)-methyl]-N-[1H-tetrazol-5-yl]-1H-imidazole-5-carboxamide
M PT. = 203 °C

EXAMPLE 26:

2-butyl-1-[(4-(phenylmethoxycarbonyl)phenyl)methyl]-N-[(4-cyanophenyl)methyl]-N-[1H-tetrazol-5-yl]-1H-imidazole-5-carboxamide
M PT. = 133 °C

EXAMPLE 27:

2-butyl-1-[(4-(1-(cyclohexyloxycarbonyloxy)ethyloxycarbonyl)phenyl)methyl]-N-[phenylmethyl]-N-[1H-tetrazol-5-yl]-1H-imidazole-5-carboxamide
M PT. = 130 °C

EXAMPLE 28:

2-butyl-1-[(4-(1-(cyclohexyloxycarbonyloxy)ethyloxycarbonyl)phenyl)methyl]-N-[(4-chlorophenyl)methyl]-N-[1H-tetrazol-5-yl]-1H-imidazole-5-carboxamide
M PT. = 164 °C

EXAMPLE 29:

2-butyl-1-[(4-(hydroxycarbonyl)phenyl)methyl]-N-[(thien-2-yl)methyl]-N-[1H-tetrazol-5-yl]-1H-imidazole-5-carboxamide.

To a suspension of 1.64 g (3.4 x 10^{-3} mole) of 2-butyl-1-[(4-(methoxycarbonyl)phenyl)methyl]-N-[(thien-2-yl)methyl]-N-[-1H-tetrazol-5-yl]-1H-imidazole-5-carboxamide, in 70 ml of methanol, is added 0.6 g (15 x 10^{-3} mole) of sodium hydroxide in solution in 6 ml of water, then this is heated to 60°C for two hours. The mixture is concentrated under reduced pressure, then the residue is solubilized in water. It is acidified by 1N hydrochloric acid until pH = 4.5. The solid obtained is filtered, washed in water and dried under vacuum in the presence of phosphoric anhydride. The raw product is recrystallized in methanol. 1.25 g in the form of white crystals is obtained (yield = 78%).

M PT. = 220°C

The following examples of products can be obtained by an operation similar to that of Example 29:

EXAMPLE 30:

1-[(4-(hydroxycarbonyl)phenyl)methyl]-2-propyl-N-[(thien-2-yl)methyl]-N-[-1H-tetrazol-5-yl]-1H-imidazole-5-carboxamide

M PT. = 243°C

EXAMPLE 31:

2-butyl-1-[(4-(hydroxycarbonyl)phenyl)methyl]-N-[phenylmethyl]-N-[1H-tetrazol-5-yl]-1H-imidazole-5-carboxamide

M PT. = 205°C

EXAMPLE 32:

2-butyl-1-[(4-(hydroxycarbonyl)phenyl)methyl]-N-[(furan-3-yl)methyl]-N-[1H-tetrazol-5-yl]-1H-imidazole-5-carboxamide

M PT. = 221°C

EXAMPLE 33:

2-butyl-1-[(4-(hydroxycarbonyl)phenyl)methyl]-N-[(4-methoxyphenyl)methyl]-N-[-1H-tetrazol-5-yl]-1H-imidazole-5-carboxamide
M PT. = 180°C

EXAMPLE 34:

2-butyl-1-[(4-(hydroxycarbonyl)phenyl)methyl]-N-[(2-chlorophenyl)methyl]-N-[-1H-tetrazol-5-yl]-1H-imidazole-5-carboxamide
M PT. = 215°C

EXAMPLE 35:

2-butyl-1-[(4-(hydroxycarbonyl)phenyl)methyl]-N-[(3-chlorophenyl)methyl]-N-[-1H-tetrazol-5-yl]-1H-imidazole-5-carboxamide
M PT. = 214°C

EXAMPLE 36:

2-butyl-1-[(4-(hydroxycarbonyl)phenyl)methyl]-N-[(4-chlorophenyl)methyl]-N-[-1H-tetrazol-5-yl]-1H-imidazole-5-carboxamide
M PT. = 180°C

EXAMPLE 37:

2-butyl-1-[(4-(hydroxycarbonyl)phenyl)methyl]-N-[(4-methylphenyl)methyl]-N-[-1H-tetrazol-5-yl]-1H-imidazole-5-carboxamide
M PT. = 184°C

EXAMPLE 38:

2-butyl-1-[(4-(hydroxycarbonyl)phenyl)methyl]-N-[(napht-2-yl)methyl]-N-[-1H-tetrazol-5-yl]-1H-imidazole-5-carboxamide
M PT. = 222°C

EXAMPLE 39:

2-butyl-1-[(4-(hydroxycarbonyl)phenyl)methyl]-N-[(3,4-dichlorophenyl)methyl]-N-[-1H-tetrazol-5-yl]-1H-imidazole-5-carboxamide
M PT. = 175°C

EXAMPLE 40:

2-butyl-1-[(4-(hydroxycarbonyl)phenyl)methyl]-N-[(4-trifluoromethyl-phenyl)methyl]-N-[-1H-tetrazol-5-yl]-1H-imidazole-5-carboxamide
M PT. = 215°C

EXAMPLE 41:

2-butyl-1-[(4-(hydroxycarbonyl)phenyl)methyl]-N-[(4-(N,N-dimethyl-amino)phenyl)methyl]-N-[-1H-tetrazol-5-yl]-1H-imidazole-5-carboxamide
M PT. = 190°C

EXAMPLE 42:

2-butyl-1-[(4-(hydroxycarbonyl)phenyl)methyl]-N-[(4-(phenylmethyloxy)phenyl)methyl]-N-[-1H-tetrazol-5-yl]-1H-imidazole-5-carboxamide
M PT. = 260°C

EXAMPLE 43:

2-butyl-1-[(4-(hydroxycarbonyl)phenyl)methyl]-N-[(4-(1-methylethyl)phenyl)methyl]-N-[-1H-tetrazol-5-yl]-1H-imidazole-5-carboxamide
M PT. = 244°C

EXAMPLE 44:

2-butyl-1-[(4-(hydroxycarbonyl)phenyl)methyl]-N-[biphenyl-4-yl-methyl]-N-[-1H-tetrazol-5-yl]-1H-imidazole-5-carboxamide
M PT. = 225°C

EXAMPLE 45:

2-butyl-1-[(4-(hydroxycarbonyl)phenyl)methyl]-N-[(4-hydroxycarbonylphenyl)methyl]-N-[-1H-tetrazol-5-yl]-1H-imidazole-5-carboxamide

M PT. = 267°C

EXAMPLE 46:

2-butyl-1-[(4-(hydroxycarbonyl)phenyl)methyl]-N-[(4-(trifluoromethyloxy)phenyl)methyl]-N-[-1H-tetrazol-5-yl]-1H-imidazole-5-carboxamide

M PT. = 204°C

EXAMPLE 47:

2-butyl-1-[(4-(hydroxycarbonyl)phenyl)methyl]-N-[(3,4-methylenedioxyphenyl)methyl]-N-[-1H-tetrazol-5-yl]-1H-imidazole-5-carboxamide

To a solution of 1.5 g (2.5×10^{-3} mole) of 2-butyl-1-[(4-(phenylmethoxycarbonyl)phenyl)methyl]-N-[(3,4-methylenedioxyphenyl)methyl]-N-[1H-tetrazol-5-yl]-1H-imidazole-5-carboxamide in 40 ml of dimethylformamide, is added under nitrogen atmosphere 0.15 g of 10% palladized charcoal. The suspension is then agitated under hydrogen atmosphere for 4 hours, under a pressure of 3.5×10^5 pascals. The catalyst is eliminated by filtration. Then water is added to the filtrate, then a 1N solution of sodium hydroxide is added to bring to alkaline pH. The aqueous phase is extracted with ethyl acetate and then is acidified with 1N hydrochloric acid until pH = 4. The precipitate product is filtered and washed in water. After recrystallization in isopropyl alcohol, 0.18 g of white crystals is obtained (yield = 14%).

M PT. = 166°C

The following example of a product can be obtained by an operation similar to that of Example 47:

EXAMPLE 48:

2-butyl-1-[(4-(hydroxycarbonyl)phenyl)methyl]-N-[(4-cyanophenyl)methyl]-N-[-1H-tetrazol-5-yl]-1H-imidazole-5-carboxamide

M PT. = 263°C

EXAMPLE 49:

2-butyl-1-[(4-(2-chlorophenylsulfonylaminocarbonyl)phenyl)methyl]-N-[(thien-2-yl)-methyl]-N-[-1H-tetrazol-5-yl]-1H-imidazole-5-carboxamide

0.63 g (1.35×10^{-3} mole) of 2-butyl-1-[(4-(hydroxycarbonyl)phenyl)methyl]-N-[(thien-2-yl)methyl]-N-[1H-tetrazol-5-yl]-1H-imidazole-5-carboxamide is suspended in 30 ml of dichloromethane. Then 0.5 g (4×10^{-3} mole) of 4-dimethylaminopyridine, 0.39 g (2×10^{-3} mole) of 2-chlorobenzenesulfonamide and 0.39 g of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride are added successively. The reaction medium is agitated at ambient temperature for 10 hours then the dichloromethane is evaporated under reduced pressure. The residue is taken up with water then acidified until pH = 3 with 1N hydrochloric acid. The precipitate is filtered, washed in water and ethanol. The precipitate is recrystallized in an ethanol-methanol mixture. 0.53 g of a white solid is obtained (yield = 61%).

M PT. = 250°C

EXAMPLE 50:

2-butyl-1-[(4-((1H-tetrazol-5-yl)aminocarbonyl)phenyl)methyl]-N-[phenylmethyl]-N-[1H-tetrazol-5-yl]-1H-imidazole-5-carboxamide

130 mg (0.8×10^{-3} mole) of 1-1'-carbonyldiimidazole is added to a solution of 320 mg (0.69×10^{-3} mole) of 2-butyl-1-[(4-(hydroxycarbonyl)phenyl)methyl]-N-[phenylmethyl]-N-[-1H-tetrazol-5-yl]-1H-imidazole-5-carboxamide, in 20 ml of tetrahydrofurane and 2 ml of dimethylformamide. The reaction mixture is brought to reflux for three hours then cooled to ambient temperature. Then 586 mg (0.69×10^{-3} mole) of 5-amino tetrazol is added. The reaction mixture is brought to reflux for

4 hours then left to return to ambient temperature for the night. The solvents are evaporated under reduced pressure, the residue is taken up with water than acidified to pH = 3 with 1N hydrochloric acid. The precipitate product is filtered, washed in water and dried. The product is recrystallized in methanol. 230 mg of white solid is obtained (yield = 64%).

M PT. = 202 °C

In the following tables I to VI, a certain number of compounds according to the invention are collected. In the tables the symbols used have the following meanings:

n-Pr = $-CH_2-CH_2-CH_3$

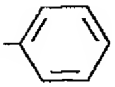
i-Pr = $-CH(CH_3)_2$

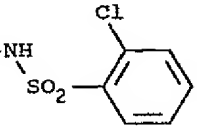
n-Bu = $-CH_2-CH_2-Ch_2-CH_3$

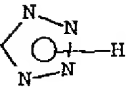
n-Pent = $-(CH_2)_4-CH_3$

DMA = $-N(CH_3)_2$

Ph = phenyl

Bn = 

OCSA = 

TA = 

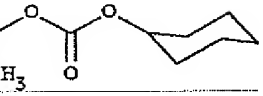
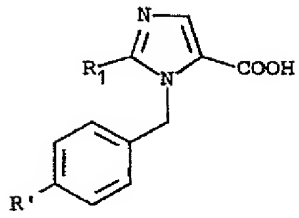
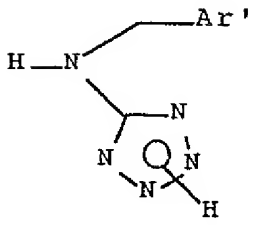
CHEC = 

Table I



PREPARATION	R_1	R'	M PT. (°C)
2	n-Bu	CO_2CH_3	212
3	n-Bu	$CO_2C_2H_5$	202
4	n-Bu	CO_2-n-Pent	168
5	n-Bu	CO_2-Bn	170
6	n-Bu	CO_2-CHEC	50
7	n-Pr	CO_2CH_3	225

Table II



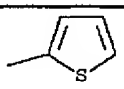
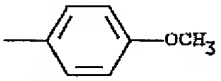
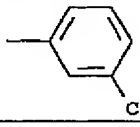
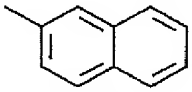
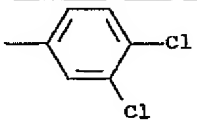
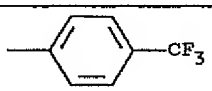
PREPARATION	Ar'	M PT. (°C)
8		210
9		186
10		230
11		208
12		234
13		220
14		226

Table II (continued)

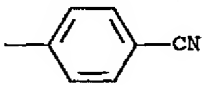
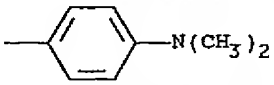
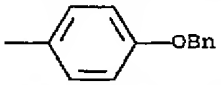
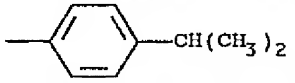
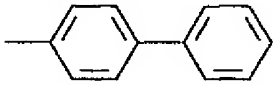
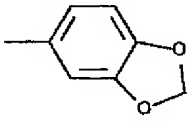
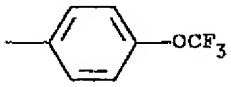
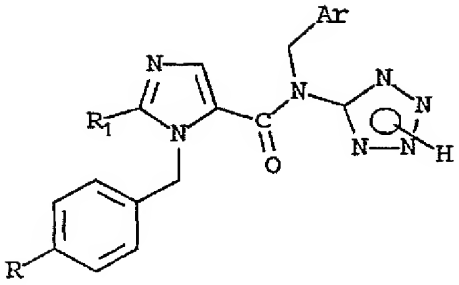
PREPARATION	Ar'	M PT. (°C)
15		230
16		213
17		223
18		205
19		260
20		220
21		224

Table III



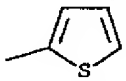
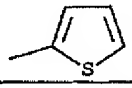
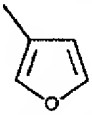
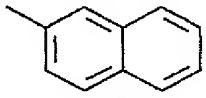
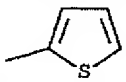
EXAMPLE	R_1	R	Ar	M PT. (°C)
1	n-Bu	CO_2CH_3		190
2	n-Pr	CO_2CH_3		191
4	n-Bu	CO_2CH_3		200
10	n-Bu	CO_2CH_3		206
21	n-Bu	$CO_2C_2H_5$		165
22	n-Bu	$CO_2C_2H_5$	Ph	184

Table III (continued)

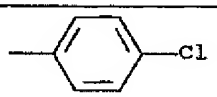
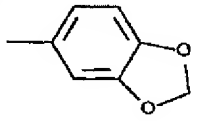
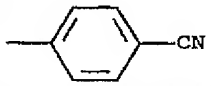
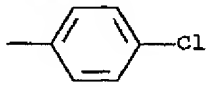
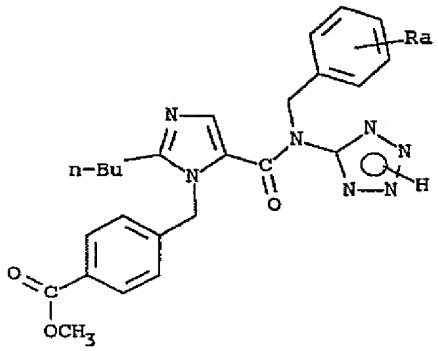
EXAMPLE	R_1	R	Ar	M PT. (°C)
23	n-Bu	CO_2-n-Pent	Ph	181
24	n-Bu	CO_2-n-Pent		191
25	n-Bu	CO_2-Bn		203
26	n-Bu	CO_2-Bn		133
27	n-Bu	CO_2-CHEC	Ph	130
28	n-Bu	CO_2-CHEC		164

Table IV

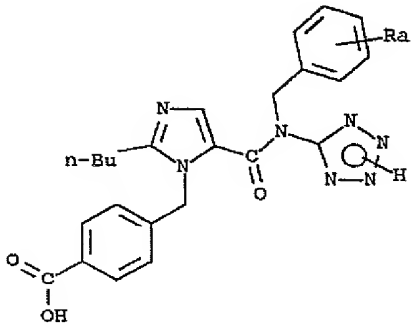


EXAMPLE	Ra	M PT. (°C)
3	H	190
5	4-OCH_3	209
6	2-Cl	151
7	3-Cl	192
8	4-Cl	204
9	4-CH_3	194
11	3,4-diCl	213
12	4-CF_3	192
13	4-DMA	170

TABLE IV (continued)

EXAMPLE	Ra	M PT. (°C)
14	4-O-Bn	202
15	4-CN	220
16	4-i-Pr	187
17	4-Ph	170
18	4-CO_2CH_3	200
19	4-OCF_3	191
20	3,4-(O-CH_2-O)	210

Table V

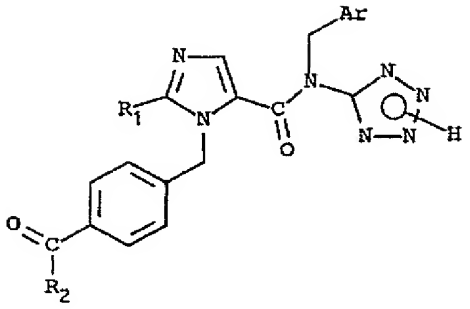


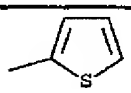
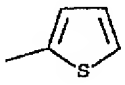
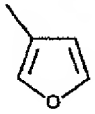
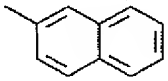
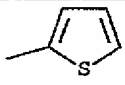
EXAMPLE	Ra	M PT. (°C)
31	H	205
33	4-OCH_3	180
34	2-Cl	215
35	3-Cl	214
36	4-Cl	180
37	4-CH_3	184
39	3,4-diCl	175
40	4-CF_3	215
41	4-DMA	190
42	4-O-Bn	260

TABLE V (continued)

EXAMPLE	Ra	M PT. (°C)
43	4-i-Pr	244
44	4-Ph	225
45	4-CO_2H	267
46	4-O-CF_3	204
47	3.4-(O-CH_2-O)	166
48	4-CN	263

Table VI



EXAMPLE	R_1	Ar	R_2	M PT. (°C)
29	n-Bu		OH	220
30	n-Pr		OH	243
32	n-Bu		OH	221
38	n-Bu		OH	222
49	n-Bu		OCSA	250
50	n-Bu	Ph	TA	202

The products according to the invention are inhibitors of the effects of angiotensin II.

The activity of the compounds according to the invention as antagonists of the angiotensin II vascular receptor was evaluated by their efficacy to antagonize the contractile response induced by angiotensin II in rabbit isolated aortic rings. The rings are suspended in a Krebs-Henseleit bath maintained at 37°C and aerated by an O_2/CO_2 mixture (95/5, V/V), then stretched at a resting tension of 2 g. After one hour of rest, a contraction is caused by angiotensin II (3×10^{-9}) in the presence of the product to be tested that was preincubated for 15 minutes. The concentration (expressed in nanomoles) of the product to be tested producing an inhibition of 50% of the contractile response (IC_{50}) is calculated from the concentration-response curve. The results obtained with a certain number of compounds according to the invention are collected in Table VII.

The compounds according to the invention have been tested on conscious normotensive rats for their propensity to inhibit a pressor response induced by angiotensin II. The compounds according to the invention were administered orally at a dose of 3 mg/kg. The results are expressed in maximum inhibition % of the pressor response to angiotensin II (Table VIII).

By way of comparison, pharmacological activity tests were also done with a known reference product presented as being a preferred angiotensin II inhibitor in patent application EP-A-425 211, and referred to as "Z" in the following tables, this Z product having the formula:

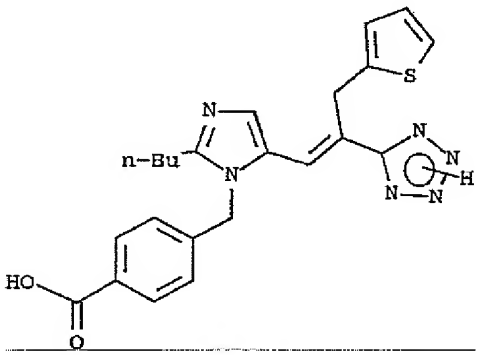


Table VII

EXAMPLE	IC_{50} ($x10^{-9}$ M)
29	1.7
31	2.2
32	2.0
33	0.5
34	3.2
35	1.6
36	0.4
37	1.7
38	5.2
39	1.0
41	4.6
49	2.7
50	2.1
Z	6.2

Table VIII

EXAMPLE	Inhibition %
1	47.9
3	54.7
29	61.8
31	72.7
Z	22.0

Reading the pharmacological test results in Tables VII and VIII shows that the products according to the invention have an angiotensin II effect inhibitory activity that is definitely higher than reference product Z.

The products according to the invention are useful in therapeutics in the treatment or prevention of high blood pressure, glaucoma, circulatory disorders, restenosis following angioplasties, the development of atheromatous or fibroproliferative lesions, diabetic nephropathy and retinopathy, infarct and angina and to improve cognitive function.

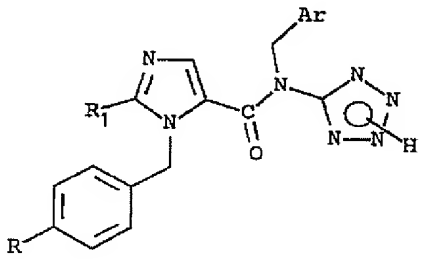
According to the invention, a therapeutic composition characterized in that the composition contains at least one compound of formula I or one of its addition salts in a therapeutically effective quantity in combination with a physiologically acceptable excipient is recommended.

The use of compounds of formula I or their addition salts as angiotensin II antagonist agents to obtain a preventive or curative medication for high blood pressure, circulatory disorders or glaucoma is also recommended.

CLAIMS

1. An imidazole-5-carboxamide compound, characterized in that the compound is chosen from the group comprised of:

(i) N-(tetrazol-5-yl)-imidazole-5-carboxamide derivatives of formula:



(I)

in which:

- R_1 represents an n-propyl or n-butyl group,
- R represents:
  * a CO_2R_2 group in which R_2 represents:
    - the hydrogen atom,
    - a C_1-C_5 linear or branched alkyl group,
    - a benzyl group,
    - a group of formula $-CH_3$-O-CO-R_4 in which R_3 represents a hydrogen atom or a methyl group and R_4 represents a C_1-C_5 linear or branched alkyl group, a C_2-C_6 linear or branched alkoxy group, or a C_5-C_6 cycloalkyloxy group,
  * a 2-chloro-phenyl-sulfonylamino-carbonyl group, or
  * a tetrazol-5-yl-amino-carbonyl group,
- Ar represents:
  * a phenyl group optionally substituted by one or more of the following atoms or groups: methyl, 1-methyl-ethyl, phenyl, chloro, cyano, methoxy, benzyloxy, trifluoromethyloxy, trifluoromethyl, N,N-dimethyl-amino, carboxyl, methoxycarbonyl,
  * a 3,4-methylenedioxy-phenyl group,
  * a 3-furanyl group,
  * a 2-thienyl group, or

* a 2-naphtyl group; and

(ii) their addition salts with mineral or organic bases

2. The compound according to Claim 1 characterized in that

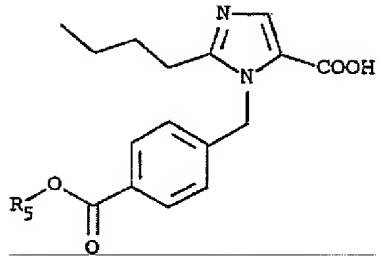
- R_1 represents an n-butyl group,
- R and Ar respectively represent the following pairs:
  * Carboxyl and 2-thienyl,
  * Carboxyl and phenyl,
  * Carboxyl and 3-furanyl,
  * Carboxyl and 4-chloro-phenyl,
  * Carboxyl and 3,4-dichloro-phenyl,
  * Carboxyl and 3-chloro-phenyl,
  * Carboxyl and 4-methyl-phenyl,
  * Carboxyl and 3,4-methylenedioxyphenyl, or
  * 1-(cyclohexyloxycarbonyloxy)-ethyloxycarbonyl and phenyl.

3. The compound according to Claim 2 characterized in that the compound is salified by an organic or mineral base.

4. A therapeutic composition characterized in that the composition contains at least one compound of formula I or one of its addition salts in a therapeutically effective quantity, in combination with a physiologically acceptable excipient.

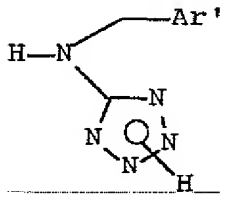
5. The use of a compound of formula I as an angiotensin II antagonist agent to obtain a preventive or curative medication for high blood pressure, circulatory disorders and glaucoma.

6. An intermediate compound, useful in the synthesis of a compound according to Claim 1, characterized in that the intermediate compound is an imidazole-5-carboxylic acid of formula:



in which R_5 represents an ethyl group, an n-pentyl group, a benzyl group or a group of formula CHR_3-O-COR_4 in which R_3 represents a hydrogen atom or a methyl group and R_4 represents a C_1-C_5 linear or branched alkyl group, a C_2-C_6 linear or branched alkoxy group or a C_5-C_6 cycloalkyloxy group.

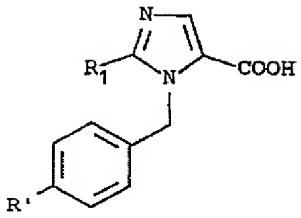
7. An intermediate compound, useful in the synthesis of a compound according to Claim 1, characterized in that the intermediate compound is a tetrazol-5-amine of formula:



in which Ar' represents a 2-thienyl group, a 2-furanyl group or a phenyl group substituted by one of the following groups: 4-methoxy, 4-trifluoromethyl, 4-cyano, 4-dimethylamino, 4-benzyloxy, 4-(1-methylethyl); 4-phenyl, 3,4-methylenedioxy, 4-trifluoromethyloxy, 3,4-dichloro.

8. A process of preparation of a compound according to Claim 1 characterized in that:

a) one cause to react a compound of formula

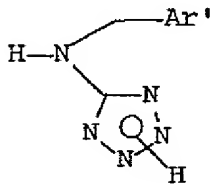


(II)

in which

- R_1 represents an n-propyl or n-butyl group,
- R' represents a $CO_2R'_2$ group in which R'_2 represents
  - a C_1-C_5 linear or branched alkyl group,
  - a benzyl group, or
  - a group of formula $-CHR_3-O-CO-R_4$ in which R_3 represents a hydrogen atom or a methyl group and R_4 represents a C_1-C_5 linear or branched alkyl group, a C_2-C_6 linear or branched alkoxy group, or a C_5-C_6 cycloalkyloxy group,

with a compound of formula:



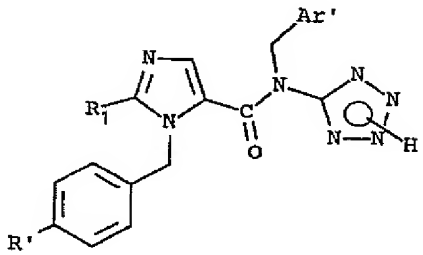
(III)

in which Ar' represents:

* a phenyl group optionally substituted by one or more of the following groups or atoms: methyl, 1-methyl-ethyl, phenyl, chloro, cyano, methoxy, benzyloxy, trifluoromethyloxy, trifluoromethyl, N,N-dimethylamino or methoxycarbonyl,
* a 3,4-(methylenedioxy)phenyl group,
* a 3-furanyl group,
* a 2-thienyl group, or
* a 2-naphtyl group,

to form an amide bond, in an organic solvent and in the presence of a catalyst, at a temperature

between ambient temperature and the reflux temperature of the reaction medium, under atmospheric pressure, for 0.5 to 24 hours, and to obtain a compound of formula:



(I')

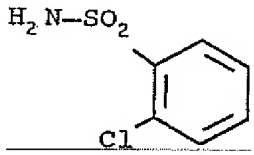
in which R_1, R' and Ar' have the same meanings as above; and,

b) if necessary, the compounds of formula I' thus obtained are subjected to the following treatments:

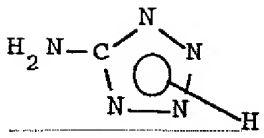
(i) a compound of formula I' is saponified, in which at least one of the R' and Ar' groups represents or contains an alkoxycarbonyl group, in the presence of a strong base in dimethoxyethane or an alcohol to obtain a compound of formula I in which at least one of the R and Ar groups represents or contains a COOH group, or

(ii) a compound of formula I' is deprotected, in which R' represents a benzyloxycarbonyl group in the presence of a catalyst to obtain a compound of formula I in which R represents a COOH group, then

(iii) one acylates an arylsulfonamide of formula:



or one acylates the 5-amino-tetrazol of formula:



by a monoacid of formula I obtained in the previous step (i) or (ii), in which R represents a COOH group and Ar has the same meanings as above for Ar' in formula III, to obtain a compound of formula I in which R_1 and Ar have the same meanings as above and R represents a 2-chlorophenylsulfonylaminocarbonyl group or a (tetrazol-5-yl)-aminocarbonyl group.

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National Registration Number

FRENCH REPUBLIC

NATIONAL INSTITUTE
OF
INDUSTRIAL PROPERTY

PRELIMINARY SEARCH REPORT

Established on the basis of the last claims filed before start of search

FA 488755
FR 9308767

DOCUMENTS CONSIDERED TO BE RELEVANT		Relevant to claim of the examined application	
Category	Citation of the document with indication, if needed, of the relevant parties		
A	CHEMICAL ABSTRACTS, Vol. 118, No. 21, 24 May 1993, Columbus, Ohio, U.S.; abstract No. 213064r, GIICHI GOTO ET AL "Preparation of five-membered heterocyclic amide derivatives" page 918; *abstract* & JP-A-04 247 081 (TAKEDA CHEMICAL INDUSTRIES) ---	1,4,5	
A	FR-A-1 585 857 (JANSSEN PHARMACEUTICA) *page 1, left column; claim 1* ---	1,4,5	
			TECHNICAL FIELDS SEARCHED (Int.Cl.5)
A	CHEMICAL ABSTRACTS, Vol. 111, No. 1, 3 July 1989, Columbus, Ohio, U.S.; abstract No. 6655z, H.P. BENECKE ET AL "Synthesis hydrolytic refractivity and initial bioevaluation of (R)-etomidate analogs. Part. Synthesis and hydrolytic refractivity of (R)-etomidate analogs" page 641; *abstract* & REPORT (CRDEC-CR-88016; ORDER NO. AD-A190763) (49 PP) 1987 compound of CN (RN): 118664-80-5 ---	1,4,5	C07D A61K
A	JOURNAL OF THE CHEMICAL SOCIETY (C). No. 4, 1971 LETCHWORTH GB pages 703-706 F. L. SCOTT ET AL "Preparation and spectra of aminotetrazoles benzylated in the nucleus or in the side-chain" *page 704* -----	7	

Date of completion of the search	Examiner
17 March 1994	Voyiazoglou, D

CATEGORY OF CITED DOCUMENTS

X: particularly relevant if taken alone
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A: relevant to at least one claim or general technological background
O: non-written disclosure
P: intermediate document

T: theory or principle underlying the invention
E: earlier patent document, but published on or after the filing date
D: cited in the application
L: cited for other reasons

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EPO FORM 1503 03.82 (PO4C13)

(19) RÉPUBLIQUE FRANÇAISE

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(51) Int Cl[6] : C 07 D 403/12 , 233/90 , 257/06 , A 61 K 31/415(C 07 D 403/12 , 233:90 , 257:06)

(12) DEMANDE DE BREVET D'INVENTION A1

(22) **Date de dépôt** : 16.07.93.

(30) **Priorité** :

(43) **Date de la mise à disposition du public de la demande :** 20.01.95 Bulletin 95/03.

(56) **Liste des documents cités dans le rapport de recherche préliminaire :** *Se reporter à la fin du présent fascicule.*

(60) **Références à d'autres documents nationaux apparentés :**

(71) **Demandeur(s) :** *Société dite: FOURNIER INDUSTRIE ET SANTE* — FR.

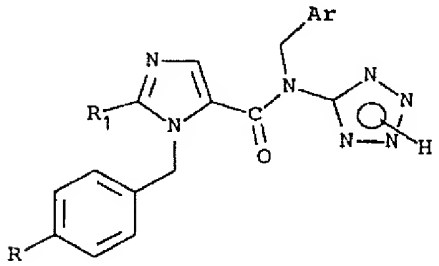
(72) **Inventeur(s) :** Dodey Pierre, Bondoux Michel, Renaut Patrice et Pruneau Didier.

(73) **Titulaire(s) :**

(74) **Mandataire :** S.A. Fedit-Loriot & Autres Conseils en Propriété Industrielle.

(54) Composés de l'imidazol-5-carboxamide, leur procédé de préparation leurs intermédiaires et leur utilisation en thérapeutique.

(57) La présente invention concerne les imidazolecarboxamides de formule:



dans laquelle les groupes R, R_1 et Ar sont définis comme indiqué dans la description.

Elle concerne également leur procédé de préparation et leur application en thérapeutique en tant qu'agents antagonistes de l'angiotensine II, utiles dans le traitement de l'hypertension, des désordres circulatoires et du glaucome.

FR 2 707 641 - A1

DOMAINE DE L'INVENTION :

La présente invention concerne des nouveaux composés de l'imidazol-5-carboxamide, leur procédé de préparation et leur utilisation en thérapeutique en tant qu'ingrédients actifs utiles dans le traitement de l'hypertension, des désordres circulatoires et du glaucome.

ART ANTERIEUR :

On connaît déjà de la littérature un certain nombre de dérivés de l'imidazole antagonistes de l'angiotensine II et utilisables en tant qu'agents antihypertenseurs. Les demandes EP-A-253 310 et EP-A-324 377 décrivent des dérivés de l'imidazole comportant de nombreuses possibilités de substituants parmi lesquels une chaîne insaturée ou des dérivés d'acide en position 5 du cycle imidazole. Les demandes de brevet EP-A-403 158, EP-A-403 159, EP-A-425 211, EP-A-535 463, EP-A-535 465 et DE-A-4132632 décrivent également des acides imidazolyl-alkénoïques portant une chaîne insaturée en position 5 du cycle imidazole; La demande WO-A-91/00277 décrit des imidazoles substitués portant une fonction aldéhyde en position 5 du cycle imidazole. La demande EP-A-427 463 décrit des dérivés substitués N-(imidazolyl) alkylalanine portant un reste amino-acide en position 5 du cycle imidazole. La demande EP-A-437 103 décrit des dérivés de l'imidazole-5-(alkyl)carboxamide substitués par des chaînes carbonées. La demande EP-A-503 785 décrit des dérivés de l'acide 1-(biphényl-méthyl)-imidazole-5-carboxylique substitués en position 4 du cycle imidazole. La demande JP-A-89 113 372 décrit des dérivés de l'imidazole-5-carboxamide doués de propriétés fongicides.

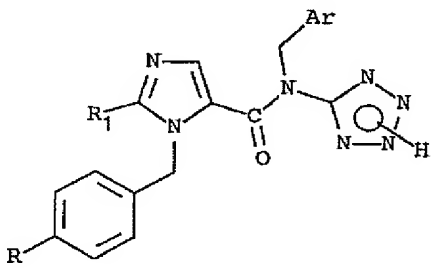
BUT DE L'INVENTION :

Aucun de ces documents antérieurs ne décrit ni ne suggère des dérivés de l'imidazole-5-carboxamide dont la fonction amide est substituée sur l'azote par un groupement tétrazolyle. Il s'est avéré que de tels dérivés montraient une excellente activité antagoniste de l'angiotensine II. La présente invention propose donc des dérivés de l'imidazole-5-carboxamide portant un groupement tétrazolyle en tant que substituant de la fonction amide.

OBJET DE L'INVENTION :

Les composés de l'invention sont caractérisés en ce qu'ils sont choisis parmi l'ensemble constitué par :

(i) les imidazole-5-carboxamides de formule :



(I)

dans laquelle :

- R_1 représente un groupe n-propyle ou n-butyle,
- R représente :
  * un groupe CO_2R_2 dans lequel R_2 représente :
    - l'atome d'hydrogène,
    - un groupe alkyle en C_1-C_5 linéaire ou ramifié,
    - un groupe benzyle,

- un groupe de formule $-CHR_3-O-CO-R_4$ dans lequel R_3 représente un atome d'hydrogène ou un groupe méthyle et R_4 représente un groupe alkyle en C_1-C_5 linéaire ou ramifié, un groupe alkoxy en C_2-C_6 linéaire ou ramifié, ou un groupe cycloalkyloxy en C_5-C_6,

* un groupe 2-chloro-phényl-sulfonylamino-carbonyle, ou

* un groupe tétrazol-5-yl-amino-carbonyle,

- Ar représente :

* un groupe phényle éventuellement substitué par un ou plusieurs des atomes ou groupes suivants : méthyle, 1-méthyl-éthyle, phényle, chloro, cyano, méthoxy, benzyloxy, trifluorométhyloxy, trifluorométhyle, N,N-diméthyl-amino, carboxyle, méthoxycarbonyle,

* un groupe 3,4-méthylènedioxyphényle,

* un groupe 3-furanyle,

* un groupe 2-thiényle, ou

* un groupe 2-naphtyle ; et

(ii) leurs sels d'addition avec des bases minérales ou organiques.

L'invention concerne également l'utilisation en thérapeutique de ces composés et leur procédé de préparation.

DESCRIPTION DETAILLEE DE L'INVENTION :

Par groupe alkyle en C_1-C_5 linéaire ou ramifié, on entend ici un groupe alkyle à chaîne hydrocarbonée, linéaire ou ramifiée comportant jusqu'à 5 atomes de carbone.
Par groupe alkoxy en C_2-C_6 linéaire ou ramifié on entend ici un groupe alkoxy dont la chaîne hydrocarbonée est linéaire ou ramifiée et comporte 2 à 6 atomes de carbone.
Par groupe cycloalkyloxy en C_5-C_6 on entend ici un groupe cyclopentyloxy, cyclopentylméthoxy ou cyclohexyloxy.

Parmi les sels d'addition avec les bases minérales et organiques, on préfèrera les sels d'addition formés avec l'hydroxyde de sodium, l'hydroxyde de potassium, l'hydroxyde de magnésium, l'hydroxyde de calcium, l'hydroxyde de lithium, la lysine, la cystéine, l'arginine, la monoéthanolamine, la méglumine, la bétaïne, la diéthylamine et la dicyclohexylamine.

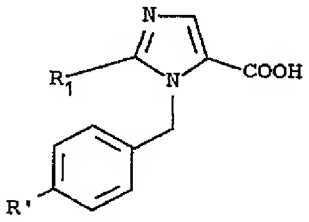
Les composés préférés de l'invention sont les composés de formule I dans laquelle :

- R_1 représente un groupe n-butyle,
- R représente un groupe carboxyle, un groupe méthoxycarbonyle ou un groupe 1-(cyclohexyloxycarbonyloxy)éthoxycarbonyle,
- Ar représente un groupe 2-thiényle, un groupe 3-furanyle ou un groupe phényle éventuellement substitué par un atome de chlore, un groupe méthyle, un groupe méthoxy, ou un groupe 3,4-méthylènedioxy,

ainsi que les sels correspondants obtenus par réaction avec une base organique ou minérale.

Les composés de formule I selon l'invention peuvent être préparés selon un procédé caractérisé en ce que :

a) on fait réagir un composé de formule :

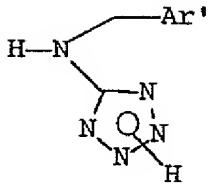


(II)

dans laquelle

- R_1 représente un groupe n-propyle ou un groupe n-butyle,
- R' représente un groupe $CO_2R'_2$ dans lequel R'_2 représente
  - un groupe alkyle en C_1-C_5, linéaire ou ramifié,
  - un groupe benzyle,
  - un groupe de formule $-CHR_3-O-CO-R_4$ dans lequel R_3 représente un atome d'hydrogène ou un groupe méthyle et R_4 représente un groupe alkyle en C_1-C_5, linéaire ou ramifié, un groupe alkoxy en C_2-C_6, linéaire ou ramifié, ou un groupe cycloalkyloxy en C_5-C_6,

avec un composé de formule :



(III)

dans laquelle Ar' représente :

* un groupe phényle éventuellement substitué par un ou plusieurs des atomes ou groupes suivants : méthyle, 1-méthyl-éthyle, phényle, chloro, cyano, méthoxy, benzyloxy, trifluorométhyloxy, trifluorométhyle, N,N-diméthylamino ou méthoxycarbonyle,

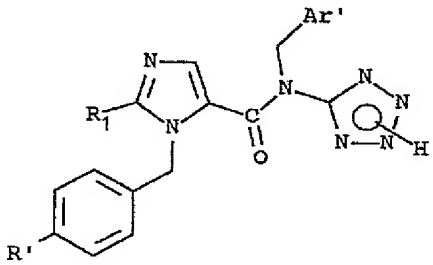
* un groupe 3,4-méthylènedioxy-phényle,

* un groupe 3-furanyle,

* un groupe 2-thiényle, ou

* un groupe 2-naphtyle,

pour former une liaison amide, selon une méthode connue en soi, dans un solvant organique, comme par exemple le tétrahydrofurane ou le diméthylformamide, et en présence d'un catalyseur d'un type connu pour former des liaisons peptidiques, comme par exemple le 1,1'-carbonyl-diimidazole (C.D.I) ou le N,N'-dicyclohexylcarbodiimide (D.C.C), à une température comprise entre la température ambiante (15-25°C) et la température de reflux du milieu réactionnel sous la pression atmosphérique, pendant 0,5 à 24 heures, et obtenir un composé de formule:



(I')

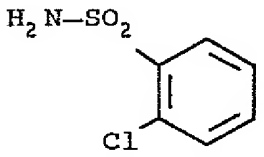
dans laquelle R_1, R' et Ar' ont les significations indiquées ci-dessus ; et,

b) si nécessaire, les composés de formule I' ainsi obtenus sont soumis aux traitements suivants:

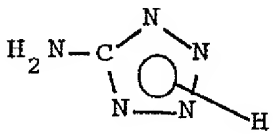
(i) on saponifie un composé de formule I' dans laquelle l'un au moins des groupes R' et Ar' représente ou contient un groupe alcoxycarbonyle, selon une méthode connue en soi, notamment en présence d'une base forte comme par exemple une solution aqueuse d'hydroxyde de sodium ou de potassium, dans le diméthoxyéthane ou un alcool comme par exemple le méthanol, pour obtenir un composé de formule I dans laquelle l'un au moins des groupes R et Ar représente ou contient un groupe COOH, ou

(ii) on déprotège un composé de formule I' dans laquelle R' représente un groupe benzyloxycarbonyl selon les méthodes connues de l'homme de l'art, notamment par hydrogénation catalytique en présence d'un catalyseur tel que du charbon palladié, pour obtenir un composé de formule I dans laquelle R représente un groupe COOH ;

(iii) on acyle une arylsulfonamide de formule :



ou le 5-amino-tétrazole de formule :



par un monoacide de formule I obtenu selon l'un des stades (i) et (ii) précédents, dans laquelle R représente un groupe COOH et Ar a les significations indiquées ci-dessus pour Ar' dans la formule III ,selon une méthode connue en soi, notamment en présence d'un réactif de couplage comme par exemple le N,N-dicyclohexylcarbodiimide ou le chlorhydrate de 1-(3-diméthylaminopropyl)-3-éthylcarbodiimide, pour obtenir un composé de formule I dans laquelle R_1 et Ar ont les significations indiquées ci-dessus et R représente un groupe 2-chlorophénylsulfonylaminocarbonyle ou un groupe (tétrazol-5-yl)-aminocarbonyle.

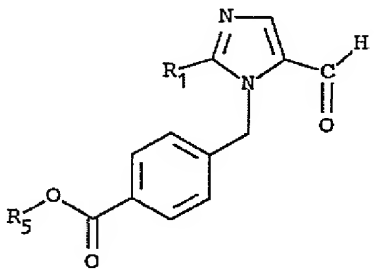
En variante on peut également obtenir les composés de formule I' ci-dessus selon un procédé caractérisé en ce que :

(i) on fait réagir un composé de formule II avec un agent halogénant comme par exemple le chlorure de thionyle pour obtenir le chlorure d'acide correspondant, puis

(ii) on fait réagir ledit chlorure d'acide avec un composé de formule III, en présence d'une base minérale comme par exemple l'hydrogénocarbonate de sodium, ou d'une base organique, comme par exemple la pyridine, pour obtenir un composé de formule I' telle que décrite ci-dessus.

Pour accéder aux composés de formule II, on préconise le procédé suivant :

on oxyde un composé de formule :



(IV)

dans laquelle R_1 représente un groupe n-propyle ou n-butyle et R_5 représente un groupe alkyle en C_1-C_5 linéaire ou ramifié, un groupe benzyle ou un groupe de formule -CHR_3-O-CO-R_4 dans laquelle R_3 et R_4 ont les mêmes significations que ci-dessus dans la formule I, selon des méthodes connues de l'homme de l'art, comme par exemple par réaction avec le chlorite de sodium, en présence d'un solvant tel qu'un mélange de 1,1-diméthyléthanol et d'eau tamponné par du phosphate monosodique, pour obtenir un composé de formule II dans laquelle R_1 représente un groupe n-propyle ou n-butyle et R' représente un groupe $CO_2R'_2$ dans lequel R'_2 représente un groupe alkyle en C_1-C_5, un groupe benzyle ou un groupe de formule -CHR_3-O-CO-R_4 dans laquelle R_3 et R_4 ont les mêmes significations que ci-dessus.

Les acides imidazole-5-carboxyliques de formule II dans laquelle R_1 représente un groupe n-propyle ou n-butyle et R' représente un groupe éthoxycarbonyle, un groupe pentyloxycarbonyle, un groupe benzyloxycarbonyle ou un groupe de formule -CO_2-CHR_3-O-COR_4 dans laquelle R_3 et R_4 ont les mêmes significations que ci-dessus, sont nouveaux et constituent l'un des objets de l'invention.

Les imidazoles-carboxaldéhydes de formule IV dans laquelle R_1 représente un groupe n- propyl ou n-butyl et R_5 représente un groupe de formule $-CHR_3-O-CO-R_4$ dans laquelle R_3 et R_4 ont les mêmes significations que ci-dessus, sont préparés par réaction d'un composé de formule IV dans laquelle R_1 a les mêmes significations que ci-dessus et R_5 représente un atome d'hydrogène, avec un dérivé halogéné de formule :

$$Cl-CHR_3-O-CO-R_4 \qquad \textbf{(V)}$$

dans laquelle R_3 et R_4 ont les mêmes significations que ci-dessus, en présence d'un agent alcalin, comme par exemple le carbonate de potassium ou l'hydrure de sodium et en présence d'un solvant.

Pour accéder aux composés de formule III, on préconise le procédé suivant :

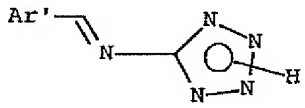
(i) on fait réagir un aldéhyde de formule :

$$Ar'-CHO$$

dans laquelle Ar' représente :

* un groupe phényle éventuellement substitué par un ou plusieurs des atomes ou groupes suivants : méthyle, 1-méthyléthyle, phényle, chloro, cyano, méthoxy, benzyloxy, trifluorométhyloxy, trifluorométhyle, N,N-diméthylamino, méthoxycarbonyle,
* un groupe 3,4-(méthylènedioxy)phényle,
* un groupe 3-furanyle,
* un groupe 2-thiényle, ou
* un groupe 2-naphtyle,

avec le 5-amino-tétrazole pour former une arylimine de formule :



dans laquelle Ar' a les mêmes significations que ci-dessus ;

(ii) on réduit l'arylimine ainsi obtenue selon une méthode connue en soi comme par exemple avec de l'hydrogène en présence d'un catalyseur, ou avec du borohydrure de sodium, dans un solvant comme par exemple le méthanol, pour obtenir un composé de formule III dans laquelle Ar' a les mêmes significations que ci-dessus.

Les aminotétrazoles de formule III dans laquelle Ar' représente :

* un groupe phényle substitué par l'un des groupes suivants :
4-méthoxy, 3,4-dichloro, 4-trifluorométhyl, 4-cyano, 4-diméthylamino, 4-benzyloxy, 4-(1-méthylèthyl), 4-phényl, 3,4-méthylènedioxy et 4-trifluorométhyloxy,
* un groupe 2-thiényle,
* un groupe 3-furanyle, ou
* un groupe 2-naphtyle,

sont nouveaux et constituent l'un des objets de l'invention. Ils interviennent en tant qu'intermédiaires de synthèse dans l'obtention de composés de formule I selon l'invention.

L'invention sera mieux comprise à la lecture des exemples de préparation suivants dans lesquels le terme "préparation" se réfère à l'obtention de tout produit intermédiaire et le terme "exemple" se réfère à l'obtention de tout produit de formule I selon l'invention. Ces éléments sont destinés à illustrer l'invention mais ne sauraient en limiter la portée.

PREPARATION 1

acide 4-[(2-butyl-5-formyl-1H-imidazol-1-yl)-méthyl]benzoïque,1-cyclohexyloxycarbonyloxy)éthyl ester

A une solution de 5,54 g (0,019 mole) d'acide 4-[(2-butyl-5-formyl-1H-imidazol-1-yl)-méthyl]benzoïque dans 25 ml de N,N-diméthylformamide (DMF) anhydre, refroidie à 0°C, sous atmosphère d'azote, on ajoute 0,63 g (0,021 mole) d'hydrure de sodium en suspension à 80% dans l'huile minérale. On agite à 0°C pendant 20 minutes puis on ajoute goutte à goutte une solution de 4 g (0,019 mole) d'acide carbonique, 1-chloroéthyl cyclohexyl ester (composé diester de formule V où R_3 est 1-chloroéthyle et R_4 est cyclohexyloxyl), dans 5 ml de DMF, puis 0,1 g ($6,6.10^{-4}$ mole) d'iodure de sodium. Le mélange réactionnel est alors agité à 90°C pendant 21 h. Après refroidissement à 0°C, on ajoute 150 ml d'eau. La phase aqueuse est acidifiée

jusqu'à pH=6,5 avec de l'acide chlorhydrique 1N et extraite par de l'acétate d'éthyle. La phase organique est lavée à l'eau, séchée sur sulfate de magnésium, filtrée et concentrée sous pression réduite. Le résidu obtenu est purifié par chromatographie sur silice en éluant avec un mélange toluène/acétate d'éthyle 90/10 puis 40/10 (V/V). On obtient 5,35 g (Rendement = 61%) d'une huile jaune.

RMN ^1H (300MHz ; $CDCl_3$; ppm)

0,79(t,3H) ; 1,19-1,63(m,12H) ; 1,61(d,3H) ; 1,82(m,2H) ; 2,63(t,2H) ; 4,54(m,1H); 5,67(s,2H) ; 6,85(q,1H) ; 7,18(d,2H) ; 7,93(d,2H) ; 7,94(s,1H) ; 9,64(s,1H).

PREPARATION 2

acide 2-butyl-1-[(4-méthoxycarbonyl-phényl)méthyl]-1H-imidazol-5-carboxylique

A une solution de 10 g (0,0333 mole) d'acide 4-[(2-butyl-5-formyl-1H-imidazol-1-yl)méthyl]benzoïque, méthyl ester, dans un mélange de 400 ml de tétrahydrofurane (THF), 400 ml de 1,1-diméthyléthanol et 170 ml d'une solution 2 M de 2-méthyl-2-butène dans le THF, on ajoute une solution de 30 g (0,333 mole) de chlorite de sodium et 30 g (0,217 mole) de dihydrogénophosphate de sodium monohydraté dans 330 ml d'eau. Le mélange réactionnel est agité à température ambiante pendant 20 heures. Le volume de solvant est réduit de 3/4 par évaporation sous pression réduite. Le solide précipité est filtré, lavé abondamment à l'eau et séché sous vide. On obtient 9,72 g (Rendement = 92%) de solide blanc.
F = 212°C

En opérant de façon analogue à la préparation 2, on obtient les produits des préparations suivantes :

PREPARATION 3

acide 2-butyl-1-[(4-éthoxycarbonyl-phényl)méthyl]-1H-imidazol-5-carboxylique
F = 202°C

PREPARATION 4

acide 2-butyl-1-[(4-pentyloxycarbonyl-phényl)méthyl]-1H-imidazol-5-carboxylique

F = 168°C

PREPARATION 5

acide 2-butyl-1-[(4-phénylméthoxycarbonyl-phényl)méthyl]-1H-imidazol-5-carboxylique.

F = 170°C

PREPARATION 6

acide 2-butyl-1-[[4-((1-(cyclohexyloxycarbonyloxy)éthyl)oxycarbonyl)phényl]méthyl]-1H-imidazol-5-carboxylique

F = 50°C

PREPARATION 7

acide 1-[(4-méthoxycarbonyl-phényl)méthyl]-2-propyl-1H-imidazol-5-carboxylique

F = 225°C

PREPARATION 8

N-(thién-2-yl-méthyl)-1H-tétrazol-5-amine

A une suspension de 2,12 g (0,025 mole) de 5-amino-2H-tétrazole dans 30 ml de méthanol anhydre, on ajoute sous atmosphère d'azote, 10 g de tamis moléculaire (0,3 nm) , 2,52 g (0,025 mole) de triéthylamine et 2,8 g (0,025 mole) de thiophène-2-carboxaldéhyde. Le mélange réactionnel est chauffé à reflux pendant 3,5 heures puis refroidi à 0°C. On ajoute alors 3 g (0,079 mole) de $NaBH_4$ par fractions et on laisse agiter pendant 3 heures à 0°C. Le méthanol est ensuite évaporé sous pression réduite. Le résidu est dilué avec 50 ml d'eau et filtré. Le filtrat est lavé à l'éther (2x25 ml) et acidifié jusqu'à pH = 3 par l'acide chlorhydrique concentré. Le précipité formé est filtré, lavé à l'eau et séché sous vide. On obtient ainsi 1,9 g (Rendement = 45 %) de solide blanc.

F = 210°C

En opérant de façon analogue à la préparation 8, on obtient les produits suivants :

PREPARATION 9

N-(furan-3-yl-méthyl)-1H-tétrazol-5-amine

F = 186°C

PREPARATION 10

N-((4-méthoxyphényl)méthyl)-1H-tétrazol-5-amine

F = 230°C

PREPARATION 11

N-((3-chlorophényl)méthyl)-1H-tétrazol-5-amine

F = 208°C

PREPARATION 12

N-(napht-2-yl-méthyl)-1H-tétrazol-5-amine

F = 234°C

PREPARATION 13

N-((3,4-dichlorophényl)méthyl)-1H-tétrazol-5-amine

F = 220°C

PREPARATION 14

N-((4-trifluorométhylphényl)méthyl)-1H-tétrazol-5-amine

F = 226°C

PREPARATION 15

N-((4-cyanophényl)méthyl)-1H-tétrazol-5-amine
F = 230°C

PREPARATION 16

N-((4-diméthylamino-phényl)méthyl)-1H-tétrazol-5-amine
F = 213°C

PREPARATION 17

N-((4-phénylméthoxy-phényl)méthyl)-1H-tétrazol-5-amine
F = 223°C

PREPARATION 18

N-((4-(1-méthyléthyl)phényl)méthyl)-1H-tétrazol-5-amine
F = 205°C

PREPARATION 19

N-((biphényl-4-yl)méthyl)-1H-tétrazol-5-amine
F = 260°C

PREPARATION 20

N-((3,4-méthylènedioxyphényl)méthyl)-1H-tétrazol-5-amine
F = 220°C

PREPARATION 21

N-((4-trifluorométhyloxy-phényl)méthyl)-1H-tétrazol-5-amine
F = 224°C

EXEMPLE 1

2-butyl-1-[(4-(méthoxycarbonyl)phényl)méthyl]-N-[(thién-2-yl)méthyl]-N-[-1H-tétrazol-5-yl]-1H-imidazol-5-carboxamide

A une suspension de 3,89 g (0,0123 mole) d'acide 2-butyl-1-[(4-(méthoxycarbonyl)phényl)méthyl]-1H-imidazol-5-carboxylique dans 190 ml de tétrahydrofurane anhydre, on ajoute sous atmosphère d'azote, 2,19 g (0,0135 mole) de 1,1'-carbonyldiimidazole. Le mélange réactionnel est porté à reflux pendant 3 heures puis on ajoute 2,45 g (0,0135 mole) de N-(thién-2-yl-méthyl)-tétrazol-5-amine. On maintient ensuite le milieu réactionnel à reflux pendant 3 heures, puis on concentre sous pression réduite. Le résidu est repris avec 100 ml d'eau et acidifié à pH = 4 avec de l'acide chlorhydrique 1N. Le précipité obtenu est filtré, rincé à l'eau et séché sous vide. Après recristallisation dans l'acétate d'éthyle, on obtient 3,22 g (Rendement = 55 %) de solide blanc en fins cristaux.

F = 190°C

En opérant de façon analogue à l'exemple 1, on obtient les produits des exemples suivants :

EXEMPLE 2 :

1-[(4-(méthoxycarbonyl)phényl)méthyl]-2-propyl-N-[(thién-2-yl)méthyl]-N-[-1H-tétrazol-5-yl]-1H-imidazol-5-carboxamide

F = 191°C

EXEMPLE 3 :

2-butyl-1-[(4-(méthoxycarbonyl)phényl)méthyl]-N-[phénylméthyl]-N-[-1H-tétrazol-5-yl]-1H-imidazol-5-carboxamide

F = 190°C

EXEMPLE 4 :

2-butyl-1-[(4-(méthoxycarbonyl)phényl)méthyl]-N-[(furan-3-yl)méthyl]-N-[-1H-tétrazol-5-yl]-1H-imidazol-5-carboxamide

F = 200°C

EXEMPLE 5 :

2-butyl-1-[(4-(méthoxycarbonyl)phényl)méthyl]-N-[(4-méthoxyphényl)méthyl]-N-[-1H-tétrazol-5-yl]-1H-imidazol-5-carboxamide

F = 209°C

EXEMPLE 6 :

2-butyl-1-[(4-(méthoxycarbonyl)phényl)méthyl]-N-[(2-chlorophényl)méthyl]-N-[-1H-tétrazol-5-yl]-1H-imidazol-5-carboxamide

F = 151°C

EXEMPLE 7 :

2-butyl-1-[(4-(méthoxycarbonyl)phényl)méthyl]-N-[(3-chlorophényl)méthyl]-N-[-1H-tétrazol-5-yl]-1H-imidazol-5-carboxamide

F = 192°C

EXEMPLE 8 :

2-butyl-1-[(4-(méthoxycarbonyl)phényl)méthyl]-N-[(4-chlorophényl)méthyl]-N-[-1H-tétrazol-5-yl]-1H-imidazol-5-carboxamide

F = 204°C

EXEMPLE 9 :

2-butyl-1-[(4-(méthoxycarbonyl)phényl)méthyl]-N-[(4-méthylphényl)méthyl]-N-[-1H-tétrazol-5-yl]-1H-imidazol-5-carboxamide

F = 194°C

EXEMPLE 10 :

2-butyl-1-[(4-(méthoxycarbonyl)phényl)méthyl]-N-[(napht-2-yl)méthyl]-N-[-1H-tétrazol-5-yl]-1H-imidazol-5-carboxamide

F = 206°C

EXEMPLE 11 :

2-butyl-1-[(4-(méthoxycarbonyl)phényl)méthyl]-N-[(3,4-dichlorophényl)méthyl]-N-[-1H-tétrazol-5-yl]-1H-imidazol-5-carboxamide

F = 213°C

EXEMPLE 12 :

2-butyl-1-[(4-(méthoxycarbonyl)phényl)méthyl]-N-[(4-trifluorométhyl-phényl)méthyl]-N-[-1H-tétrazol-5-yl]-1H-imidazol-5-carboxamide

F = 192°C

EXEMPLE 13 :

2-butyl-1-[(4-(méthoxycarbonyl)phényl)méthyl]-N-[(4-(N,N-diméthylamino)-phényl)méthyl]-N-[-1H-tétrazol-5-yl]-1H-imidazol-5-carboxamide

F = 170°C

EXEMPLE 14 :

2-butyl-1-[(4-(méthoxycarbonyl)phényl)méthyl]-N-[(4-(phénylméthoxy)phényl)-méthyl]-N-[-1H-tétrazol-5-yl]-1H-imidazol-5-carboxamide

F = 202°C

EXEMPLE 15 :

2-butyl-1-[(4-(méthoxycarbonyl)phényl)méthyl]-N-[(4-cyanophényl)méthyl]-N-[-1H-tétrazol-5-yl]-1H-imidazol-5-carboxamide

F = 220°C

EXEMPLE 16 :

2-butyl-1-[(4-(méthoxycarbonyl)phényl)méthyl]-N-[(4-(1-méthyléthyl)phényl)méthyl]-N-[-1H-tétrazol-5-yl]-1H-imidazol-5-carboxamide

F = 187°C

EXEMPLE 17 :

2-butyl-1-[(4-(méthoxycarbonyl)phényl)méthyl]-N-[biphényl-4-yl-méthyl]-N-[-1H-tétrazol-5-yl]-1H-imidazol-5-carboxamide

F = 170°C

EXEMPLE 18 :

2-butyl-1-[(4-(méthoxycarbonyl)phényl)méthyl]-N-[(4-(méthoxycarbonyl)phényl)-méthyl]-N-[-1H-tétrazol-5-yl]-1H-imidazol-5-carboxamide

F = 200 °C

EXEMPLE 19 :

2-butyl-1-[(4-(méthoxycarbonyl)phényl)méthyl]-N-[(4-(trifluorométhyloxy)phényl)-méthyl]-N-[-1H-tétrazol-5-yl]-1H-imidazol-5-carboxamide

F = 191°C

EXEMPLE 20 :

2-butyl-1-[(4-(méthoxycarbonyl)phényl)méthyl]-N-[(3,4-méthylènedioxyphényl)-méthyl]-N-[-1H-tétrazol-5-yl]-1H-imidazol-5-carboxamide

F = 210°C

EXEMPLE 21 :

2-butyl-1-[(4-(éthoxycarbonyl)phényl)méthyl]-N-[(thién-2-yl)méthyl]-N-[1H-tétrazol-5-yl]-1H-imidazol-5-carboxamide

F = 165°C

EXEMPLE 22 :

2-butyl-1-[(4-(éthoxycarbonyl)phényl)méthyl]-N-[phénylméthyl]-N-[1H-tétrazol-5-yl]-1H-imidazol-5-carboxamide

F = 184°C

EXEMPLE 23 :

2-butyl-1-[(4-(pentyloxycarbonyl)phényl)méthyl]-N-[phénylméthyl]-N-[1H-tétrazol-5-yl]-1H-imidazol-5-carboxamide

F = 181°C

EXEMPLE 24 :

2-butyl-1-[(4-(pentyloxycarbonyl)phényl)méthyl]-N-[(4-chlorophényl)méthyl]-N-[1H-tétrazol-5-yl]-1H-imidazol-5-carboxamide

F = 191°C

EXEMPLE 25 :

2-butyl-1-[(4-(phénylméthoxycarbonyl)phényl)méthyl]-N-[(3,4-méthylènedioxyphényl)-méthyl]-N-[1H-tétrazol-5-yl]-1H-imidazol-5-carboxamide

F = 203°C

EXEMPLE 26 :

2-butyl-1-[(4-(phénylméthoxycarbonyl)phényl)méthyl]-N-[(4-cyanophényl)méthyl]-N-[1H-tétrazol-5-yl]-1H-imidazol-5-carboxamide

F = 133°C

EXEMPLE 27 :

2-butyl-1-[(4-(1-(cyclohexyloxycarbonyloxy)éthyloxycarbonyl)phényl)méthyl]-N-[phénylméthyl]-N-[1H-tétrazol-5-yl]-1H-imidazol-5-carboxamide

F = 130°C

EXEMPLE 28 :

2-butyl-1-[(4-(1-(cyclohexyloxycarbonyloxy)éthyloxycarbonyl)phényl)méthyl]-N-[(4-chlorophényl)méthyl]-N-[1H-tétrazol-5-yl]-1H-imidazol-5-carboxamide

F = 164°C

EXEMPLE 29 :

2-butyl-1-[(4-(hydroxycarbonyl)phényl)méthyl]-N-[(thien-2-yl)méthyl]-N-[1H-tétrazol-5-yl]-1H-imidazol-5-carboxamide,

A une suspension de 1,64 g ($3,4.10^{-3}$ mole) de 2-butyl-1-[(4-(méthoxycarbonyl)phényl)méthyl]-N-[(thién-2-yl)méthyl]-N-[-1H-tétrazol-5-yl]-1H-imidazol-5-carboxamide, dans 70 ml de méthanol, on ajoute 0,6 g (15.10^{-3} mole) d'hydroxyde de sodium en solution dans 6 ml d'eau, puis on chauffe à 60°C pendant deux heures. On concentre sous pression réduite, puis le résidu est solubilisé dans de l'eau. On acidifie par de l'acide chlorhydrique 1N jusqu'à pH = 4,5. Le solide obtenu est filtré, lavé à l'eau et séché sous vide en présence d'anhydride phosphorique. Le produit brut est recristallisé dans le méthanol. On obtient 1,25 g (Rendement = 78 %) sous forme de cristaux blancs.
F = 220°C

En opérant de façon analogue à l'exemple 29, on obtient les produits des exemples suivants :

EXEMPLE 30 :

1-[(4-(hydroxycarbonyl)phényl)méthyl]-2-propyl-N-[(thién-2-yl)méthyl]-N-[-1H-tétrazol-5-yl]-1H-imidazol-5-carboxamide
F = 243°C

EXEMPLE 31 :

2-butyl-1-[(4-(hydroxycarbonyl)phényl)méthyl]-N-[phénylméthyl]-N-[-1H-tétrazol-5-yl]-1H-imidazol-5-carboxamide
F = 205°C

EXEMPLE 32 :

2-butyl-1-[(4-(hydroxycarbonyl)phényl)méthyl]-N-[(furan-3-yl)méthyl]-N-[-1H-tétrazol-5-yl]-1H-imidazol-5-carboxamide
F = 221°C

EXEMPLE 33 :

2-butyl-1-[(4-(hydroxycarbonyl)phényl)méthyl]-N-[(4-méthoxyphényl)méthyl]-N-[-1H-tétrazol-5-yl]-1H-imidazol-5-carboxamide

F = 180°C

EXEMPLE 34 :

2-butyl-1-[(4-(hydroxycarbonyl)phényl)méthyl]-N-[(2-chlorophényl)méthyl]-N-[-1H-tétrazol-5-yl]-1H-imidazol-5-carboxamide

F = 215°C

EXEMPLE 35 :

2-butyl-1-[(4-(hydroxycarbonyl)phényl)méthyl]-N-[(3-chlorophényl)méthyl]-N-[-1H-tétrazol-5-yl]-1H-imidazol-5-carboxamide

F = 214°C

EXEMPLE 36 :

2-butyl-1-[(4-(hydroxycarbonyl)phényl)méthyl]-N-[(4-chlorophényl)méthyl]-N-[-1H-tétrazol-5-yl]-1H-imidazol-5-carboxamide

F = 180°C

EXEMPLE 37 :

2-butyl-1-[(4-(hydroxycarbonyl)phényl)méthyl]-N-[(4-méthylphényl)méthyl]-N-[-1H-tétrazol-5-yl]-1H-imidazol-5-carboxamide

F = 184°C

EXEMPLE 38 :

2-butyl-1-[(4-(hydroxycarbonyl)phényl)méthyl]-N-[(napht-2-yl)méthyl]-N-[-1H-tétrazol-5-yl]-1H-imidazol-5-carboxamide

F = 222°C

EXEMPLE 39 :

2-butyl-1-[(4-(hydroxycarbonyl)phényl)méthyl]-N-[(3,4-dichlorophényl)méthyl]-N-[-1H-tétrazol-5-yl]-1H-imidazol-5-carboxamide

F = 175°C

EXEMPLE 40 :

2-butyl-1-[(4-(hydroxycarbonyl)phényl)méthyl]-N-[(4-trifluorométhyl-phényl)méthyl]-N-[-1H-tétrazol-5-yl]-1H-imidazol-5-carboxamide

F = 215°C

EXEMPLE 41 :

2-butyl-1-[(4-(hydroxycarbonyl)phényl)méthyl]-N-[(4-(N,N-diméthyl-amino)phényl)méthyl]-N-[-1H-tétrazol-5-yl]-1H-imidazol-5-carboxamide

F = 190°C

EXEMPLE 42 :

2-butyl-1-[(4-(hydroxycarbonyl)phényl)méthyl]-N-[(4-(phénylméthyloxy)phényl) méthyl]-N-[-1H-tétrazol-5-yl]-1H-imidazol-5-carboxamide

F = 260°C

EXEMPLE 43 :

2-butyl-1-[(4-(hydroxycarbonyl)phényl)méthyl]-N-[(4-(1-méthyléthyl)phényl)méthyl]-N-[-1H-tétrazol-5-yl]-1H-imidazol-5-carboxamide

F = 244°C

EXEMPLE 44 :

2-butyl-1-[(4-(hydroxycarbonyl)phényl)méthyl]-N-[biphényl-4-yl-méthyl]-N-[-1H-tétrazol-5-yl]-1H-imidazol-5-carboxamide

F = 225°C

EXEMPLE 45 :

2-butyl-1-[(4-(hydroxycarbonyl)phényl)méthyl]-N-[(4-hydroxycarbonylphényl)méthyl]-N-[-1H-tétrazol-5-yl]-1H-imidazol-5-carboxamide

F = 267°C

EXEMPLE 46 :

2-butyl-1-[(4-(hydroxycarbonyl)phényl)méthyl]-N-[(4-(trifluorométhyloxy)phényl) méthyl]-N-[-1H-tétrazol-5-yl]-1H-imidazol-5-carboxamide

F = 204°C

EXEMPLE 47

2-butyl-1-[(4-(hydroxycarbonyl)phényl)méthyl]-N-[(3,4-méthylènedioxyphényl) méthyl]-N-[1H-tétrazol-5-yl]-1H-imidazol-5-carboxamide.

A une solution de 1,5 g (2,5.10-3 mole) de 2-butyl-1-[(4-(phénylméthoxycarbonyl)phényl)méthyl]-N-[(3,4-méthylènedioxyphényl)méthyl]-N-[1H-tétrazol-5-yl]-1H-imidazol-5-carboxamide dans 40 ml de diméthylformamide, on ajoute sous atmosphère d'azote 0,15 g de charbon palladié à 10 %. La suspension est agitée ensuite sous atmosphère d'hydrogène pendant 4 heures, sous une pression de $3,5.10^5$ Pascals. On élimine le catalyseur par filtration. On ajoute ensuiste de l'eau au filtrat, puis on ajoute une solution 1N d'hydroxyde de sodium pour amener à pH alcalin. On extrait avec de l'acétate d'éthyle puis on acidifie la phase aqueuse avec de l'acide chlorhydrique 1N, jusqu'à pH = 4. Le produit précipite et on filtre et lave à l'eau. Après recristallisation dans l'alcool isopropylique on obtient 0,18 g de cristaux blancs (Rendement = 14 %).

F = 166°C

En opérant de façon analogue à l'exemple 47 on prépare le produit de l'exemple suivant :

EXEMPLE 48 :

2-butyl-1-[(4-(hydroxycarbonyl)phényl)méthyl]-N-[(4-cyanophényl)méthyl]-N-[-1H-tétrazol-5-yl]-1H-imidazol-5-carboxamide

F = 263°C

EXEMPLE 49 :

2-butyl-1-[(4-(2-chlorophénylsulfonylaminocarbonyl)phényl)méthyl]-N-[(thién-2-yl)-méthyl]-N-[-1H-tétrazol-5-yl]-1H-imidazol-5-carboxamide

On met en suspension 0,63 g ($1,35.10^{-3}$ mole) de 2-butyl-1-[(4-(hydroxycarbonyl)phényl)méthyl]-N-[(thién-2-yl)méthyl]-N-[1H-tétrazol-5-yl]-1H-imidazol-5-carboxamide, dans 30 ml de chlorure de méthylène. On ajoute successivement 0,5 g (4.10^{-3} mole) de 4-diméthylaminopyridine, 0,39 g (2.10^{-3} mole) de 2-chlorobenzènesulfonamide et 0,39 g chlorydrate de 1-(3-diméthylaminopropyl)-3-éthylcarbodiimide. Le milieu réactionnel est agité à température ambiante pendant 10 heures puis on évapore le chlorure de méthylène sous pression réduite. On reprend le résidu à l'eau puis on acidifie jusqu'à pH = 3 avec de l'acide chlorhydrique 1N. Le précipité est filtré, lavé à l'eau et à l'éthanol. On le recristallise dans un mélange éthanol-méthanol. On obtient 0,53 g (Rendement = 61 %) de solide blanc.

F = 250°C.

EXEMPLE 50 :

2-butyl-1-[(4-((1H-tétrazol-5-yl)aminocarbonyl)phényl)méthyl]-N-[phénylméthyl]-N-[1H-tétrazol-5-yl]-1H-imidazol-5-carboxamide.

On ajoute 130 mg ($0,8.10^{-3}$ mole) de 1-1'-carbonyldiimidazole à une solution de 320 mg ($0,69.10^{-3}$ mole) de 2-butyl-1-[(4-(hydroxycarbonyl)phényl)méthyl]-N-[phénylméthyl]-N-[-1H-tétrazol-5-yl]-1H-imidazol-5-carboxamide, dans 20 ml de tétrahydrofurane et 2 ml de diméthylformamide. On porte le milieu réactionnel à reflux pendant trois heures puis on refroidit jusqu'à température ambiante. On ajoute alors 586 mg ($0,69.10^{-3}$ mole) de 5-aminotétrazole. On porte le milieu réactionnel à reflux pendant 4 heures puis on laisse revenir à température ambiante pendant la

nuit. On évapore les solvants sous pression réduite, on reprend le résidu avec de l'eau puis on acidifie à pH = 3 avec de l'acide chlorhydrique 1N. Le produit précipité est filtré, lavé à l'eau et séché. On le recristallise dans le méthanol. On obtient 230 mg (Rendement = 64 %) de solide blanc.

F = 202°C.

On a regroupé dans les tableaux I à VI suivants un certain nombre de composés selon l'invention. Dans les tableaux les symboles utilisés ont les significations suivantes :

n-Pr = $-CH_2-CH_2-CH_3$

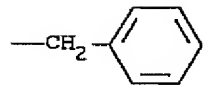
i-Pr = $-CH(CH_3)_2$

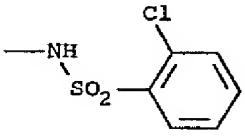
n-Bu = $-CH_2-CH_2-CH_2-CH_3$

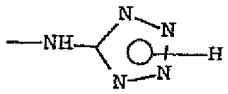
n-Pent = $-(CH_2)_4-CH_3$

DMA = $-N(CH_3)_2$

Ph = phényl

Bn = 

OCSA = 

TA = 

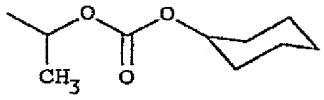
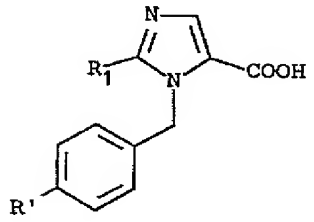
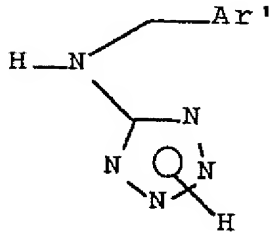
CHEC = 

Tableau I



PREPARATION	R_1	R'	F(°C)
2	n-Bu	CO_2CH_3	212
3	n-Bu	$CO_2C_2H_5$	202
4	n-Bu	CO_2-n-Pent	168
5	n-Bu	CO_2-Bn	170
6	n-Bu	CO_2-CHEC	50
7	n-Pr	CO_2CH_3	225

Tableau II



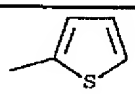
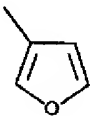
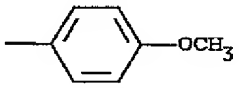
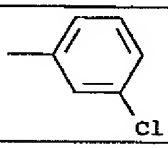
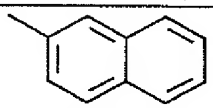
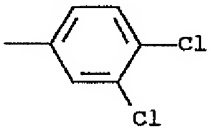
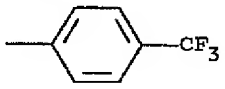
PREPARATION	Ar'	F(°C)
8		210
9		186
10		230
11		208
12		234
13		220
14		226

Tableau II (suite)

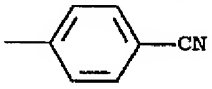
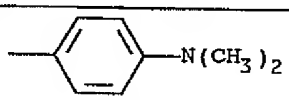
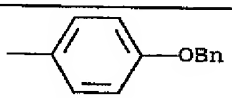
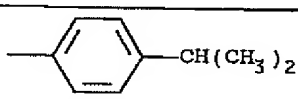
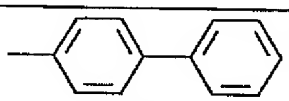
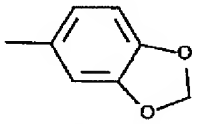
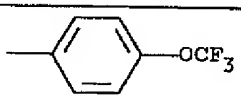
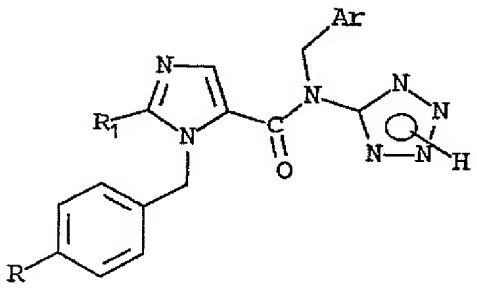
PREPARATION	Ar'	F(°C)
15		230
16		213
17		223
18		205
19		260
20		220
21		224

Tableau III



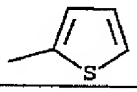
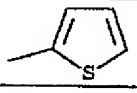
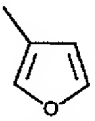
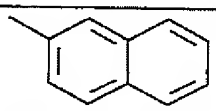
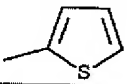
EXEMPLE	R_1	R	Ar	F(°C)
1	n-Bu	CO_2CH_3		190
2	n-Pr	CO_2CH_3		191
4	n-Bu	CO_2CH_3		200
10	n-Bu	CO_2CH_3		206
21	n-Bu	$CO_2C_2H_5$		165
22	n-Bu	$CO_2C_2H_5$	Ph	184

Tableau III (suite)

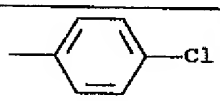
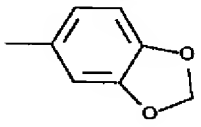
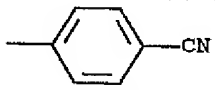
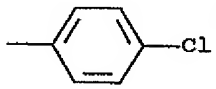
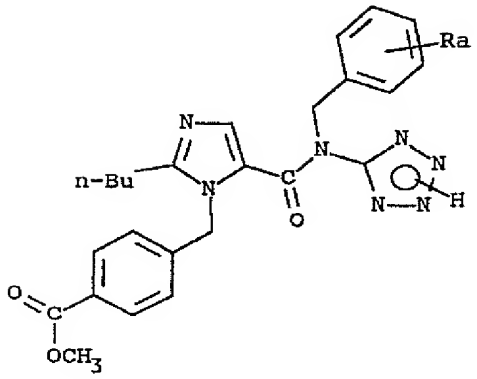
EXEMPLE	R_1	R	Ar	F(°C)
23	n-Bu	CO_2-n-Pent	Ph	181
24	n-Bu	CO_2-n-Pent		191
25	n-Bu	CO_2-Bn		203
26	n-Bu	CO_2-Bn		133
27	n-Bu	CO_2-CHEC	Ph	130
28	n-Bu	CO_2-CHEC		164

Tableau IV

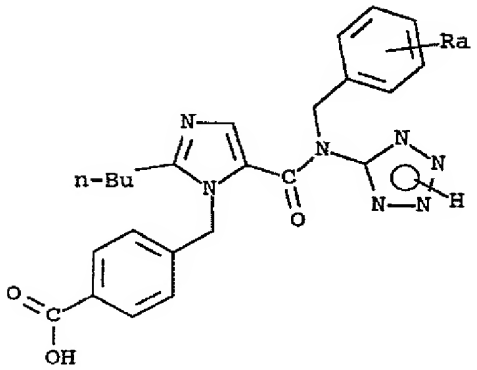


EXEMPLE	Ra	F(°C)
3	H	190
5	4-OCH_3	209
6	2-Cl	151
7	3-Cl	192
8	4-Cl	204
9	4-CH_3	194
11	3,4-diCl	213
12	4-CF_3	192
13	4-DMA	170

TABLEAU IV (suite)

EXEMPLE	Ra	F(°C)
14	4-O-Bn	202
15	4-CN	220
16	4-i-Pr	187
17	4-Ph	170
18	4-CO_2CH_3	200
19	4-OCF_3	191
20	3,4-(O-CH_2-O)	210

Tableau V

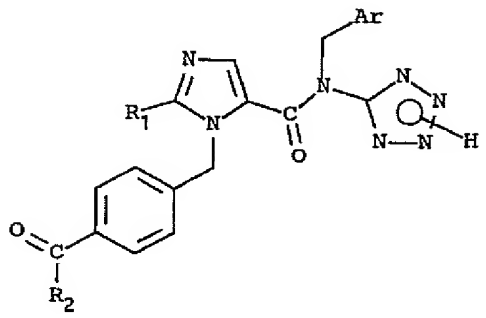


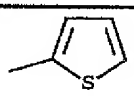
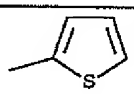
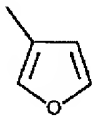
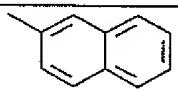
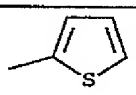
EXEMPLE	Ra	F(°C)
31	H	205
33	4-OCH_3	180
34	2-Cl	215
35	3-Cl	214
36	4-Cl	180
37	4-CH_3	184
39	3,4-diCl	175
40	4-CF_3	215
41	4-DMA	190
42	4-O-Bn	260

TABLEAU V (suite)

EXEMPLE	Ra	F(°C)
43	4-i-Pr	244
44	4-Ph	225
45	4-CO_2H	267
46	4-O-CF_3	204
47	3,4-(O-CH_2-O)	166
48	4-CN	263

Tableau VI



EXEMPLE	R_1	Ar	R_2	F(°C)
29	n-Bu		OH	220
30	n-Pr		OH	243
32	n-Bu		OH	221
38	n-Bu		OH	222
49	n-Bu		OCSA	250
50	n-Bu	Ph	TA	202

Les produits selon l'invention sont des inhibiteurs des effets de l'angiotensine II.

L'activité des composés selon l'invention comme antagonistes du récepteur vasculaire de l'angiotensine II a été évaluée par leur efficacité à antagoniser la réponse contractile induite par l'angiotensine II dans des anneaux isolés d'aorte de lapin. Les anneaux sont suspendus dans un bain de Krebs-Henseleit maintenu à 37°C et aéré par un mélange O_2/CO_2 (95/5, V/V) puis étirés à une tension de repos de 2g. Après une heure de repos, on provoque une contraction par l'angiotensine II (3.10^{-9} M) en présence du produit à tester préincubé pendant 15 minutes. La concentration (exprimée en nanomole) de produit à tester produisant une inhibition de 50 % de la réponse contractile (IC_{50}) est calculée à partir de la courbe concentration-réponse. Les résultats obtenus avec un certain nombre de composés selon l'invention sont regroupés dans le tableau VII.

Les composés selon l'invention ont été testés chez le rat normotendu conscient pour leur propension à inhiber une réponse pressive induite par l'angiotensine II. Les composés selon l'invention ont été administrés oralement à la dose de 3 mg/kg. Les résultats sont exprimés en % maximum d'inhibition de la réponse pressive à l'angiotensine II (Tableau VIII).

A titre de comparaison, les tests d'activité pharmacologique ont été faits également avec un produit de référence connu et présenté comme étant un inhibiteur préféré de l'angiotensine II dans la demande de brevet EP-A-425 211, et appelé "Z" dans les tableaux qui suivent, ce produit Z ayant pour formule :

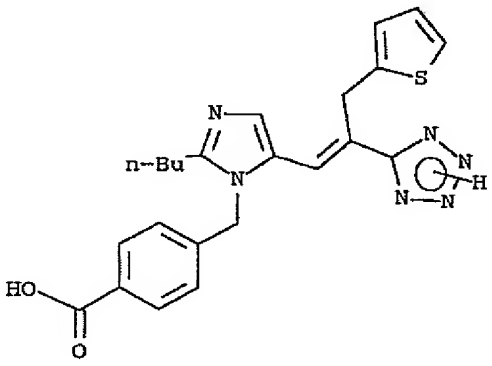


Tableau VII

EXEMPLE	IC_{50} ($x10^{-9}$ M)
29	1,7
31	2,2
32	2,0
33	0,5
34	3,2
35	1,6
36	0,4
37	1,7
38	5,2
39	1,0
41	4,6
49	2,7
50	2,1
Z	6,2

Tableau VIII

EXEMPLE	% inhibition
1	47,9
3	54,7
29	61,8
31	72,7
Z	22,0

La lecture des résultats des tests pharmacologiques dans les tableaux VII et VIII montre que les produits selon l'invention présentent une activité inhibitrice des effets de l'angiotensine II nettement supérieure au produit de référence Z.

Les produits selon l'invention sont utiles en thérapeutique dans le traitement ou la prévention de l'hypertension artérielle, du glaucome, des désordres circulatoires, des resténoses consécutives aux angioplasties, des développements de lésions athéromateuses ou fibrinoprolifératives, des néphropaties et rétinopathies d'origine diabétique, de l'infarctus, de l'angor et pour l'amélioration de la fonction cognitive.

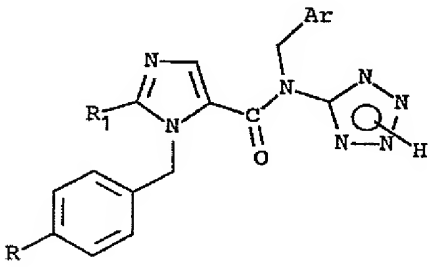
Selon l'invention on préconise une composition thérapeutique caractérisée en ce qu'elle renferme au moins un composé de formule I ou l'un de ses sels d'addition en quantité thérapeutiquement efficace en association avec un excipient physiologiquement acceptable.

On préconise également l'utilisation des composés de formule I ou de leurs sels d'addition, en tant qu'agents antagonistes de l'angiotensine II, pour l'obtention d'un médicament préventif ou curatif de l'hypertension artérielle, des désordres circulatoires et du glaucome.

REVENDICATIONS

1. Composé imidazole-5-carboxamide, caractérisé en ce qu'il est choisi parmi l'ensemble constitué par :

(i) les dérivés de N-(tétrazol-5-yl)-imidazol-5-carboxamide de formule :



(I)

dans laquelle :

- R_1 représente un groupe n-propyle ou n-butyle,
- R représente :
  * un groupe CO_2R_2 dans lequel R_2 représente :
    - l'atome d'hydrogène,
    - un groupe alkyle en C_1-C_5 linéaire ou ramifié,
    - un groupe benzyle,
    - un groupe de formule $-CHR_3-O-CO-R_4$ dans lequel R_3 représente un atome d'hydrogène ou un groupe méthyle et R_4 représente un groupe alkyle en C_1-C_5 linéaire ou ramifié, un groupe alkoxy en C_2-C_6 linéaire ou ramifié, ou un groupe cycloalkyloxy en C_5-C_6,
  * un groupe 2-chloro-phényl-sulfonylamino-carbonyle, ou
  * un groupe tétrazol-5-yl-amino-carbonyle,
- Ar représente :
  * un groupe phényle éventuellement substitué par un ou plusieurs des atomes ou groupes suivants : méthyle, 1-méthyl-éthyle, phényle, chloro, cyano, méthoxy, benzyloxy, trifluorométhyloxy, trifluorométhyle, N,N-diméthyl-amino, carboxyle, méthoxycarbonyle,
  * un groupe 3,4-méthylènedioxy-phényle,
  * un groupe 3-furanyle,
  * un groupe 2-thiényle, ou

* un groupe 2-naphtyle ; et

(ii) leurs sels d'addition avec des bases minérales ou organiques

2. Composé selon la revendication 1 caractérisé en ce que

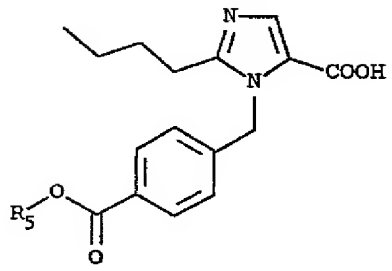
- R_1 représente un groupe n-butyle,
- R et Ar représentent respectivement les couples suivants :
  * carboxyle et 2-thiényle,
  * carboxyle et phényle,
  * carboxyle et 3-furanyle,
  * carboxyle et 4-chloro-phényl,
  * carboxyle et 3,4-dichloro-phényle,
  * carboxyle et 3-chloro-phényle,
  * carboxyle et 4-méthyl-phényle,
  * carboxyle et 3,4-méthylènedioxyphényle, ou
  * 1-(cyclohexyloxycarbonyloxy)-éthyloxycarbonyle et phényle.

3. Composé selon la revendication 2 caractérisé en ce qu'il est salifié par une base organique ou minérale.

4. Composition thérapeutique caractérisée en ce qu'elle renferme au moins un composé de formule I ou l'un de ses sels d'addition en quantité thérapeutiquement efficace, en association avec un excipient physiologiquement acceptable.

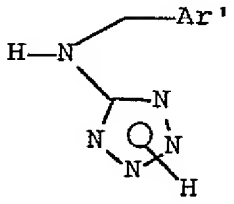
5. Utilisation d'un composé selon la revendication 1, en tant qu'agent antagoniste de l'angiotensine II, pour l'obtention d'un médicament préventif ou curatif de l'hypertension artérielle, des désordres circulatoires et du glaucome.

6. Composé intermédiaire, utile dans la synthèse d'un composé selon la revendication 1, caractérisé en ce qu'il s'agit d'un acide imidazol-5-carboxylique de formule :



dans laquelle R_5 représente un groupe éthyle, un groupe n-pentyle, un groupe benzyle ou un groupe de formule CHR_3-O-COR_4 dans laquelle R_3 représente un atome d'hydrogène ou un groupe méthyle et R_4 représente un goupe alkyle en C_1-C_5 linéaire ou ramifié, un groupe alkoxy en C_2-C_6 linéaire ou ramifié ou un groupe cycloalkyloxy en C_5-C_6.

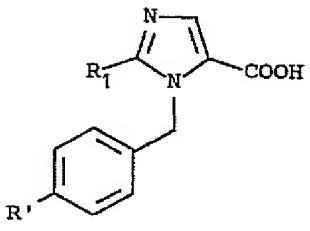
7. Composé intermédiaire, utile dans la synthèse d'un composé selon la revendication 1, caractérisé en ce qu'il s'agit d'une tétrazole-5-amine de formule :



dans laquelle Ar' représente un groupe 2-thiényle, un groupe 2-furanyle ou un groupe phényle substitué par l'un des groupes suivants : 4-méthoxy, 4-trifluorométhyle, 4-cyano, 4-diméthylamino, 4-benzyloxy, 4-(1-méthyléthyl); 4-phényle, 3,4-méthylènedioxy, 4-trifluorométhyloxy, 3,4-dichloro.

8. Procédé de préparation d'un composé selon la revendication 1 caractérisé en ce que :

a) on fait réagir un composé de formule

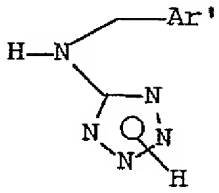


(II)

dans laquelle

- R_1 représente un groupe n-propyle ou un groupe n-butyle,
- R' représente un groupe $CO_2R'_2$ dans lequel R'_2 représente
  - un groupe alkyle en C_1-C_5, linéaire ou ramifié,
  - un groupe benzyle, ou
  - un groupe de formule $-CHR_3-O-CO-R_4$ dans lequel R_3 représente un atome d'hydrogène ou un groupe méthyle et R_4 représente un groupe alkyle en C_1-C_5, linéaire ou ramifié, un groupe alkoxy en C_2-C_6, linéaire ou ramifié, ou un groupe cycloalkyloxy en C_5-C_6,

avec un composé de formule :



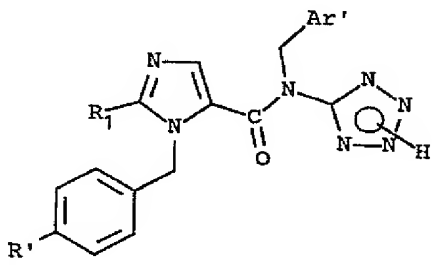
(III)

dans laquelle Ar' représente :

* un groupe phényle éventuellement substitué par un ou plusieurs des atomes ou groupes suivants : méthyle, 1-méthyl-éthyle, phényle, chloro, cyano, méthoxy, benzyloxy, trifluorométhyloxy, trifluorométhyle, N,N-diméthylamino ou méthoxycarbonyle,
* un groupe 3,4-(méthylènedioxy)phényl,
* un groupe 3-furanyle,
* un groupe 2-thiényle, ou
* un groupe 2-naphtyle,

pour former une liaison amide, dans un solvant organique et en présence d'un catalyseur, à une température comprise entre la température ambiante et la

température de reflux du milieu réactionnel, sous la pression atmosphérique, pendant 0,5 à 24 heures, et obtenir un composé de formule:



(I')

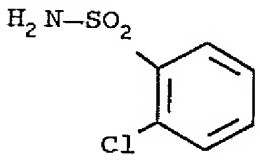
dans laquelle R_1, R' et Ar' ont les significations indiquées ci-dessus ; et,

b) si nécessaire, on soumet les composés de formule I' ainsi obtenus aux traitements suivants:

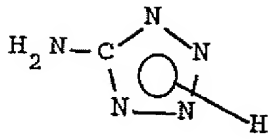
(i) on saponifie un composé de formule I' dans laquelle l'un au moins des groupes R' et Ar' représente ou contient un groupe alcoxycarbonyle, en présence d'une base forte dans le diméthoxyéthane ou un alcool pour obtenir un composé de formule I dans laquelle l'un au moins des groupes R et Ar représente ou contient un groupe COOH, ou

(ii) on déprotège un composé de formule I' dans laquelle R' représente un groupe benzyloxycarbonyl, en présence d'un catalyseur, pour obtenir un composé de formule I dans laquelle R représente un groupe COOH, puis

(iii) on acyle une arylsulfonamide de formule :



ou le 5-amino-tétrazole de formule :



par un monoacide de formule I obtenu au stade (i) ou (ii) précédent, dans laquelle R représente un groupe COOH et Ar a les significations indiquées ci-dessus pour Ar' dans la formule III, pour obtenir un composé de formule I dans laquelle R_1 et Ar ont les significations indiquées ci-dessus et R représente un groupe 2-chlorophénylsulfonylaminocarbonyle ou un groupe (tétrazol-5-yl)-aminocarbonyle.

REPUBLIQUE FRANÇAISE

INSTITUT NATIONAL
de la
PROPRIETE INDUSTRIELLE

RAPPORT DE RECHERCHE PRELIMINAIRE

établi sur la base des dernières revendications déposées avant le commencement de la recherche

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N° d'enregistrement national

FA 488755
FR 9308767

DOCUMENTS CONSIDERES COMME PERTINENTS

Catégorie	Citation du document avec indication, en cas de besoin, des parties pertinentes	Revendications concernées de la demande examinée
A	CHEMICAL ABSTRACTS, vol. 118, no. 21, 24 Mai 1993, Columbus, Ohio, US; abstract no. 213064r, GIICHI GOTO ET AL 'Preparation of five-membered heterocyclic amide derivatives' page 918 ; * abrégé * & JP-A-04 247 081 (TAKEDA CHEMICAL INDUSTRIES)	1,4,5
A	FR-A-1 585 857 (JANSSEN PHARMACEUTICA) * page 1, colonne de gauche; revendication 1 *	1,4,5
A	CHEMICAL ABSTRACTS, vol. 111, no. 1, 3 Juillet 1989, Columbus, Ohio, US; abstract no. 6655z, H. P. BENECKE ET AL 'Synthesis hydrolytic refractivity and initial bioevaluation of (R)-etomidate analogs. Part . Synthesis and hydrolytic refractivity of (R)-etomidate analogs' page 641 ; * abrégé * & REPORT (CRDEC-CR-88016; ORDER NO. AD-A190763)(49 PP) 1987 composé du CN (RN): 118664-80-5	1,4,5
A	JOURNAL OF THE CHEMICAL SOCIETY (C). no. 4 , 1971 , LETCHWORTH GB pages 703 - 706 F. L. SCOTT ET AL 'Preparation and spectra of aminotetrazoles benzylated in the nucleus or in the side-chain' * page 704 *	7

DOMAINES TECHNIQUES RECHERCHES (Int.Cl.5)

C07D
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Date d'achèvement de la recherche	Examinateur
17 Mars 1994	Voyiazoglou, D

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(12) # PATENT APPLICATION A1

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(30) **Priority:**

(43) **Date Application Made Available to the Public:**
20/01/95 Bulletin 95/03.

(56) **List of Documents Cited in the Search Report:**
Refer to the end of the present fascicule.

(60) **Reference(s) to Other Related Domestic Documents:**

(71) **Applicant(s):** *Company known as: FOURNIER INDUSTRIE ET SANTE* – FR.

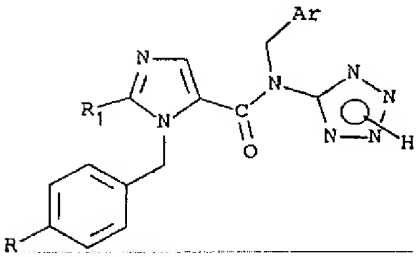
(72) **Inventor(s):** Dodey Pierre, Bondoux Michel, Renaut Patrice and Pruneau Didier.

(73) **Grantee(s):**

(74) **Agent(s):** S.A. Fedit-Loriot & Autres Conseils en Propriété Industrielle.

(54) **Imidazole-5-carboxamide compounds, their process of preparation, their intermediates and their use in therapeutics.**

(57) The present invention relates to the imidazolecarboxamides of formula:



in which the R, R1 and Ar groups are defined as indicated in the description. The invention also relates to their process of preparation and their application in therapeutics as antagonist agents for angiotensin II, useful in the treatment of hypertension, circulatory disorders and glaucoma.

FR 2 707 641-A1

[bar code]

FIELD OF THE INVENTION:

The present invention relates to novel imidazole-5-carboxamide compounds, their process of preparation and their use in therapeutics as active ingredients useful in the treatment of hypertension, circulatory disorders and glaucoma.

PRIOR ART:

A certain number of imidazole angiotensin II antagonist derivatives usable as antihypertensive agents are already known in the literature. Applications EP-A-253 310 and EP-A-324 377 describe imidazole derivatives comprising numerous substituent possibilities, including an unsaturated chain or acid derivatives in Position 5 of the imidazole ring. Patent applications EP-A-403 158, EP-A-403 159, EP-A-425 211, EP-A-535 463, EP-A-535 465 and DE-A-4132632 also describe imidazolyl-alkenoic acids with an unsaturated chain in Position 5 of the imidazole ring; application WO-A-91/00277 describes substituted imidazoles with an aldehyde function in Position 5 of the imidazole ring. Application EP-A-427 463 describes substituted N-(imidazolyl) alkyl alanine derivatives with an amino acid residue in Position 5 of the imidazole ring. Application EP-A-437 103 describes imidazole-5-(alkyl)carboxamide derivatives substituted by carbon chains. Application EP-A-503 785 describes derivatives of 1-(biphenyl-methyl)-imidazole-5-carboxylic acid substituted in position 4 of the imidazole ring. Application JP-A-89 113 372 describes derivatives of imidazole-5-carboxamide with fungicide properties.

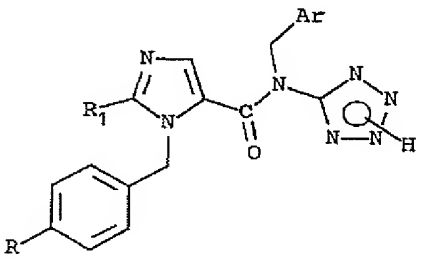
GOAL OF THE INVENTION:

None of these prior documents describes or suggests derivatives of imidazole-5-carboxamide whose amide function is substituted on nitrogen by a tetrazolyl group. It turns out that such derivatives demonstrate excellent angiotensin II antagonist activity. Thus, the present invention proposes derivatives of imidazole-5-carboxamide with a tetrazolyl group as the substituent for the amide function.

OBJECT OF THE INVENTION:

The compounds of the invention are characterized in that they are chosen from among the group comprised of:

(i) imidazole-5-carboxamides of formula:



(I)

in which:

- R_1 represents an n-propyl or n-butyl group,
- R represents:
  - * a CO_2R_2 group in which R_2 represents:
    - the hydrogen atom,
    - a C_1-C_5 linear or branched alkyl group,
    - a benzyl group,

- a group of formula $-CHR_3-O-CO-R_4$ in which R_3 represents a hydrogen atom or a methyl group and R_4 represents a C_1-C_5 linear or branched alkyl group, a C_2-C_6 linear or branched alkoxy group or a C_5-C_6 cycloalkyloxy group.

* a 2-chloro-phenyl-sulfonylamino-carbonyl group, or

* a tetrazol-5-yl-amino-carbonyl group,

- Ar represents:

* A phenyl group optionally substituted by one or more of the following atoms or groups: methyl, 1-methyl-ethyl, phenyl, chloro, cyano, methoxy, benzyloxy, trifluoromethyloxy, trifluoromethyl, N,N-dimethyl-amino, carboxyl, methylcarbonyl,

* A 3,4-methylenedioxyphenyl group,

* A 3-furanyl group,

* A 2-thienyl group, or

* A 2-naphtyl group; and

(ii) their addition salts with mineral or organic bases.

The invention also relates to the use in therapeutics of these compounds and their process of preparation.

DETAILED DESCRIPTION OF THE INVENTION:

C_1-C_5 linear or branched alkyl group here is understood to refer to an alkyl group with a linear or branched hydrocarbon chain comprising up to 5 carbon atoms. C_2-C_6 linear or branched alkoxy group here is understood to refer to an alkoxy group whose hydrocarbon chain is linear or branched and comprises 2 to 6 carbon atoms.

C_5-C_6 cycloalkyloxy group here is understood to refer to a cyclopentyloxy, cyclopentylmethoxy or cyclohexyloxy group.

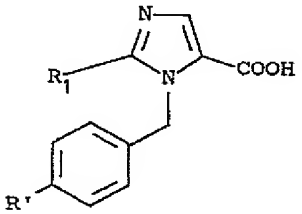
From the addition salts with mineral and organic bases, addition salts formed with sodium hydroxide, potassium hydroxide, magnesium hydroxide, calcium hydroxide, lithium hydroxide, lysine, cysteine, arginine, monoethanolamine, meglumine, betaine, diethylamine and dicyclohexylamine will be preferred.

The preferred compounds of the invention are the compounds of formula I in which:

- R_1 represents an n-butyl group,
- R represents a carboxyl group, a methoxycarbonyl group or a 1-(cyclohexyloxycarbonyloxy)ethoxycarbonyl group,
- Ar represents a 2-thienyl group, a 3-furanyl group or a phenyl group optionally substituted by a chlorine atom, a methyl group, a methoxy group, or a 3,4-methylenedioxy group, as well as the corresponding salts obtained by reaction with an organic or mineral base.

The compounds of formula I according to the invention may be prepared according to a process characterized in that:

a) a compound of formula:

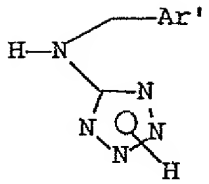


(II)

is caused to react, in which

- R_1 represents an n-propyl or n-butyl group,
- R' represents a $CO_2R'_2$ group in which R'_2 represents
  - A C_1-C_5 linear or branched alkyl group,
  - A benzyl group,
  - A group of formula $-CHR_3-O-CO-R_4$ in which R_3 represents a hydrogen atom or a methyl group and R_4 represents a C_1-C_5 linear or branched alkyl group, a C_2-C_6 linear or branched alkoxy group, or a C_5-C_6 cycloalkyloxy group,

with a compound of formula:

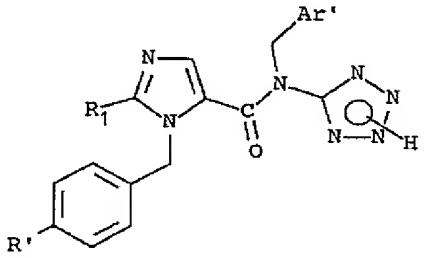


(III)

in which Ar' represents:

* a phenyl group optionally substituted by one or more of the following atoms or groups: methyl, 1-methyl-ethyl, phenyl, chloro, cyano, methoxy, benzyloxy, trifluoromethyloxy, trifluoromethyl, N,N-dimethylamino or methoxycarbonyl,
* a 3,4-methylenedioxy-phenyl group,
* a 3-furanyl group,
* a 2-thienyl group, or
* a 2-naphtyl group,

to form an amide bond, according to a method known in itself, in an organic solvent, such as for example tetrahydrofurane or dimethylformamide, and in the presence of a catalyst of a known type to form peptide bonds, such as for example 1,1'-carbonyl-diimidazole (C.D.I.) or N,N'-dicyclohexylcarbodiimide (D.C.C.), at a temperature between ambient temperature (15-25°C) and the reflux temperature of the reaction medium under atmospheric pressure for 0.5 to 24 hours and to obtain a compound of formula:



(I')

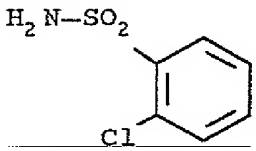
in which R_1, R' and Ar' have the same meanings as above; and

b) if necessary, the compounds of formula I' thus obtained are subjected to the following treatments:

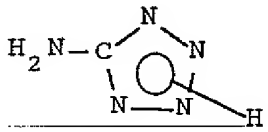
(i) saponifying a compound of formula I' in which at least one of the R' and Ar' groups represents or contains an alkoxycarbonyl group, according to a method known in itself, particularly in the presence of a strong base such as for example an aqueous sodium or potassium hydroxide, in dimethoxyethane or an alcohol such as for example methanol, to obtain a compound of formula I in which at least one of the R and Ar groups represents or contains a COOH group, or

(ii) deprotecting a compound of formula I' in which R' represents a benzyloxycarbonyl group according to methods known to the person skilled in the art, particularly by catalytic hydrogenation in the presence of a catalyst such as palladized charcoal, to obtain a compound of formula I in which R represents a COOH group;

(iii) acylating an arylsulfonamide of formula:



or 5-amino-tetrazol of formula:



by a monoacid of formula I obtained according to one of the previous steps (i) and (ii), in which R represents a COOH group and Ar has the same meanings as above for Ar' in formula III, according to a method known in itself, particularly in the presence of a coupling reagent such as for example N,N-dicyclohexylcarbodiimide or 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride, to obtain a compound of formula I in which R_1 and Ar have the same meanings as above and R represents a 2-chlorophenylsulfonylaminocarbonyl group or a (tetrazol-5-yl)-aminocarbonyl group.

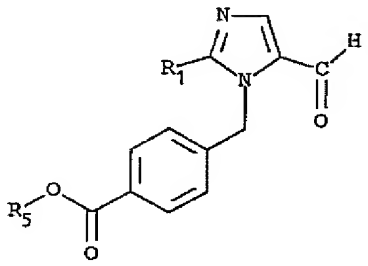
In a variation, one may also obtain the compounds of formula I' above according to a process characterized in that:

(i) a compound of formula II is caused to react with a halogenating agent such as for example thionyl chloride to obtain the corresponding acid chloride, then

(ii) said acid chloride is caused to react with a compound of formula III, in the presence of a mineral base such as for example sodium hydrogencarbonate, or an organic base, such as for example pyridine, to obtain a compound of formula I' such as described above.

To access the compounds of formula II, the following process is recommended:

one oxidizes a compound of formula:



(IV)

in which R_1 represents an n-propyl or n-butyl group and R_5 represents a C_1-C_5 linear or branched alkyl group, a benzyl group or a group of formula $-CHR_3$-O-CO-R_4 in which R_3 and R_4 have the same meanings as above in formula I, according to processes known to the person skilled in the art, such as for example by reaction with sodium chlorite, in the presence of a solvent such as a mixture of 1,1-dimethylethanol and water buffered with monosodium phosphate to obtain a compound of formula II in which R_1 represents an n-propyl or n-butyl group and R' represents a $CO_2R'_2$ group in which R'_2 represents a C_1-C_5 alkyl group, a benzyl group or a group of formula -CHR_3 -O-CO-R_4 in which R_3 and R_4 have the same meanings as above. The imidazole-5-carboxylic acids of formula II in which R_1 represents an n-propyl or n-butyl group and R' represents an ethoxycarbonyl group, a pentyloxycarbonyl group, a benzyloxycarbonyl group or a group of formula -CO_2-CHR_3 -O-CO-R_4 in which R_3 and R_4 have the same meanings as above, are novel and constitute one of the objects of the invention.

The imidazoles-carboxaldehydes of formula IV in which R_1 represents an n-propyl or n-butyl group and R_5 represents a group of formula $-CHR_3-O-CO-R_4$ in which R_3 and R_4 have the same meanings as above, are prepared by reaction of a compound of formula IV in which R_1 has the same meanings as above and R_5 represents a hydrogen atom, with a halogen derivative of formula:

$$Cl-CHR_3-O-CO-R_4 \qquad (V)$$

in which R_3 and R_4 have the same meanings as above, in the presence of an alkaline agent, such as for example potassium carbonate or sodium hydride in the presence of a solvent.

To access the compounds of formula III, the following process is recommended:

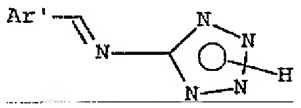
(i) one causes to react an aldehyde of formula:

Ar'-CHO

in which Ar' represents:

* a phenyl group optionally substituted by one or more of the following atoms or groups: methyl, 1-methylethyl, phenyl, chloro, cyano, methoxy, benzyloxy, trifluoromethyloxy, trifluoromethyl, N,N-dimethylamino, methoxycarbonyl,
* a 3,4-(methylenedioxy)phenyl group,
* a 3-furanyl group,
* a 2-thienyl group, or
* a 2-naphtyl group,

with 5-amino-tetrazol to form an arylimine of formula:



in which Ar' has the same meanings as above;

(ii) the arylamine thus obtained is reduced according to a method known in itself such as for example with hydrogen in the presence of a catalyst, or with sodium borohydride, in a solvent such as for example methanol to obtain a compound of formula III in which Ar' has the same meanings as above.

The amino tetrazols of formula III in which Ar' represents:

* a phenyl group substituted by one of the following groups: 4-methoxy, 3,4-dichloro, 4-trifluoromethyl, 4-cyano, 4-dimethylamino, 4-benzyloxy, 4-(1-methylethyl), 4-phenyl, 3,4-methylenedioxy and 4-trifluoromethyloxy,
* a 2-thienyl group,
* a 3-furanyl group, or
* a 2-naphtyl group,

are novel and constitute one of the objects of the invention. They are involved as synthesis intermediates in obtaining compounds of formula I according to the invention.

The invention will be better understood upon reading the following examples of preparation in which the term "preparation" refers to obtaining any intermediate product and the term "example" refers to obtaining any product of formula I according to the invention. These elements are intended to illustrate the invention but should not limit its scope.

PREPARATION 1

4-[(2-butyl-5-formyl-1H-imidazole-1-yl)-methyl]benzoic, 1-cyclohexyloxycarbonyloxy)ethyl ester acid

To a solution of 5.54 g (0.019 mole) of 4-[(2-butyl-5-formyl-1H-imidazole-1-yl)-methyl]benzoic acid in 25 ml of anhydrous N,N-dimethylformamide (DMF), cooled to 0°C, under nitrogen atmosphere, is added 0.63 g (0.021 mole) of sodium hydride in 80% suspension in mineral oil. This is agitated at 0°C for 20 minutes then a solution of 4 g (0.019 mole) carbonic acid, 1-chloroethyl cyclohexyl ester (diester compound of formula V where R_3 is 1-chloroethyl and R_4 is cyclohexyloxy), in 5 ml of DMF, then 0.1 g (6.6×10^{-4} mole) of sodium iodide is added dropwise. The reaction mixture is then agitated at 90°C for 21 hours. After cooling to 0°C, 150 ml of water is added. The aqueous

phase is acidified up to pH = 6.5 with 1N hydrochloric acid and extracted by ethyl acetate. The organic phase is washed with water, dried by magnesium sulfate, filtered and concentrated under reduced pressure. The residue obtained is purified by silica chromatography by elution with a 90/10 then 40/10 toluene/ethyl acetate mixture (V/V). 5.35 g of a yellow oil is obtained (yield = 61%).

NMR ^1H (300 MHz; $CDCl_3$; ppm)

0.79(t, 3H); 1.19-1.63 (m, 12H); 1.61(d, 3H); 1.82 (m, 2H); 2.63(t, 2H); 4.54 (m, 1H); 5.67 (s, 2H); 6.85 (q, 1H); 7.18 (d, 2H); 7.93 (d, 2H); 7.94 (s, 1H); 9.64 (s, 1H).

PREPARATION 2

2-butyl-1-[(4-methoxycarbonyl-phenyl)methyl]-1H-imidazole-5-carboxylic acid

To a solution of 10 g (0.0333 mole) of 4-[2-butyl-5-formyl-1H-imidazole-1-yl)methyl]benzoic, methyl ester acid, in a mixture of 400 ml of tetrahydrofurane (THF), 400 ml of 1,1-dimethylethanol and 170 ml of a 2 M solution of 2-methyl-2-butene in THF, is added a solution of 30 g (0.333 mole) of sodium chlorite and 30 g (0.217 mole) of monohydrated sodium dihydrogen phosphate in 330 ml of water. The reaction mixture is agitated at ambient temperature for 20 hours. The solvent volume is reduced by ¾ by evaporation under reduced pressure. The solid precipitate is filtered, washed thoroughly in water and dried under vacuum. 9.72 g of a white solid is obtained (yield = 92%).
M PT. = 212°C.

The following preparation products can be obtained by an operation similar to that of Preparation 2:

PREPARATION 3

2-butyl-1-[(4-ethoxycarbonyl-phenyl)methyl]-1H-imidazole-5-carboxylic acid
M PT. = 202°C

PREPARATION 4

2-butyl-1-[(4-pentyloxycarbonyl-phenyl)methyl]-1H-imidazole-5-carboxylic acid

M PT. = 168 °C

PREPARATION 5

2-butyl-1-[(4-phenylmethoxycarbonyl-phenyl)methyl]-1H-imidazole-5-carboxylic acid

M PT. = 170 °C

PREPARATION 6

2-butyl-1-[(4-((1-(cyclohexyloxycarbonyloxy)ethyl)oxycarbonyl)phenyl)methyl]-1H-imidazole-5-carboxylic acid

M PT. = 50 °C

PREPARATION 7

1-[(4-methoxycarbonyl-phenyl)methyl]-2-propyl-1H-imidazole-5-carboxylic acid

M PT. = 225 °C

PREPARATION 8

N-(thien-2-yl-methyl)-1H-tetrazol-5-amine

To a suspension of 2.12 g (0.025 mole) of 5-amino-2H-tetrazol in 30 ml of anhydrous methanol is added, under nitrogen atmosphere, 10 g of molecular sieve (0.3 nm), 2.52 g (0.025 mole) of trimethylamine and 2.8 g (0.025 mole) of thiophene-2-carboxaldehyde. The reaction mixture is heated to reflux for 3.5 hours then cooled to 0 °C. Then 3 g (0.079 mole) of $NaBH_4$ is added by fractions and left to agitate for 3 hours at 0 °C. The methanol is then evaporated under reduced pressure. The residue is diluted with 50 ml of water and filtered. The filtrate is washed with ether (2 x 25 ml) and acidified up to pH = 3 by concentrated hydrochloric acid. The precipitate formed is filtered, washed in water and dried under vacuum. Thus 1.9 g of a white solid is obtained (yield = 45%).

M PT. = 210 °C

The following products are obtained by an operation similar to that of Preparation 8:

PREPARATION 9

N-(furan-3-yl-methyl)-1H-5-amine
M PT. = 186°C

PREPARATION 10

N-((4-methyoxyphenyl)methyl)-1H-tetrazol-5-amine
M PT. = 230°C

PREPARATION 11

N-((3-chlorophenyl)methyl)-1H-tetrazol-5-amine
M PT. = 208°C

PREPARATION 12

N-(napht-2-yl-methyl)-1H-tetrazol-5-amine
M PT. = 234°C

PREPARATION 13

N-((3,4-dichlorophenyl)methyl)-1H-tetrazol-5-amine
M PT. = 220°C

PREPARATION 14

N-((4-trifluoromethylphenyl)methyl)-1H-tetrazol-5-amine
M PT. = 226°C

PREPARATION 15

N-((4-cyanophenyl)methyl)-1H-tetrazol-5-amine
M PT. = 230°C

PREPARATION 16

N-((4-dimethylamino-phenyl)methyl)-1H-tetrazol-5-amine
M PT. = 213°C

PREPARATION 17

N-((4-phenylmethoxy-phenyl)methyl)-1H-tetrazol-5-amine
M PT. = 223°C

PREPARATION 18

N-((4-(1-methylethyl)phenyl)methyl)-1H-tetrazol-5-amine
M PT. = 205°C

PREPARATION 19

N-((biphenyl-4-yl)methyl)-1H-tetrazol-5-amine
M PT. = 260°C

PREPARATION 20

N-((3,4-methylenedioxyphenyl)methyl)-1H-tetrazol-5-amine
M PT. = 220°C

PREPARATION 21

N-((4-trifluoromethyloxy-phenyl)methyl)-1H-tetrazol-5-amine
M PT. = 224°C

EXAMPLE 1

2-butyl-1-[(4-(methyoxycarbonyl)phenyl)methyl]-N-[(thien-2-yl)methyl]-N-[-1H-tetrazol-5-yl]-1H-imidazole-5-carboxamide

To a suspension of 3.89 g (0.0123 mole) of 2-butyl-1-[(4-(methoxycarbonyl)phenyl)methyl]-1H-imidazole-5-carboxylic acid in 190 ml of anhydrous tetrahydrofurane, is added, under nitrogen atmosphere, 2.19 g (0.0135 mole) of 1,1'-carbonyldiimidazole. The reaction mixture is brought to reflux for 3 hours then 2.45 g (0.0135 mole) of N-(thien-2-yl-methyl)-tetrazol-5-amine is added. The reaction mixture is then maintained at reflux for 3 hours, and then concentrated under reduced pressure. The residue is taken up with 100 ml of water and acidified at pH = 4 with 1N hydrochloric acid. The precipitate obtained is filtered, rinsed in water and dried under vacuum. After recrystallization in ethyl acetate, 3.22 g of a white solid in fine crystals is obtained (yield = 55%).
M PT. = 190°C

The following examples of products can be obtained by an operation similar to that of Example 1:

EXAMPLE 2:

1-[(4-(methoxycarbonyl)phenyl)methyl]-2-propyl-N-[(thien-2-yl)methyl]-N-[-1H-tetrazol-5-yl]-1H-imidazole-5-carboxamide
M PT. = 191°C

EXAMPLE 3:

2-butyl-1-[(4-(methoxycarbonyl)phenyl)methyl]-N-[-1H-tetrazol-5-yl]-1H-imidazole-5-carboxamide
M PT. = 190°C

EXAMPLE 4:

2-butyl-1-[(4-(methoxycarbonyl)phenyl)methyl]-N-[(furan-3-yl)methyl]-N-[-1H-tetrazol-5-yl]-1H-imidazole-5-carboxamide
M PT. = 200°C

EXAMPLE 5:

2-butyl-1-[(4-(methoxycarbonyl)phenyl)methyl]-N-[(4-methoxyphenyl)methyl]-N-[-1H-tetrazol-5-yl]-1H-imidazole-5-carboxamide
M PT. = 209 °C

EXAMPLE 6:

2-butyl-1-[(4-(methoxycarbonyl)phenyl)methyl]-N-[(2-chlorophenyl)methyl]-N-[-1H-tetrazol-5-yl]-1H-imidazole-5-carboxamide
M PT. = 151 °C

EXAMPLE 7:

2-butyl-1-[(4-(methoxycarbonyl)phenyl)methyl]-N-[(3-chlorophenyl)methyl]-N-[-1H-tetrazol-5-yl]-1H-imidazole-5-carboxamide
M PT. = 192 °C

EXAMPLE 8:

2-butyl-1-[(4-(methoxycarbonyl)phenyl)methyl]-N-[(4-chlorophenyl)methyl]-N-[-1H-tetrazol-5-yl]-1H-imidazole-5-carboxamide
M PT. = 204 °C

EXAMPLE 9:

2-butyl-1-[(4-(methoxycarbonyl)phenyl)methyl]-N-[(4-methylphenyl)methyl]-N-[-1H-tetrazol-5-yl]-1H-imidazole-5-carboxamide
M PT. = 194 °C

EXAMPLE 10:

2-butyl-1-[(4-(methoxycarbonyl)phenyl)methyl]-N-[(napht-2-yl)methyl]-N-[-1H-tetrazol-5-yl]-1H-imidazole-5-carboxamide
M PT. = 206 °C

EXAMPLE 11:

2-butyl-1-[(4-(methoxycarbonyl)phenyl)methyl]-N-[(3,4-dichlorophenyl)methyl]-N-[-1H-tetrazol-5-yl]-1H-imidazole-5-carboxamide
M PT. = 213°C

EXAMPLE 12:

2-butyl-1-[(4-(methoxycarbonyl)phenyl)methyl]-N-[(4-trifluoromethyl-phenyl)methyl]-N-[-1H-tetrazol-5-yl]-1H-imidazole-5-carboxamide
M PT. = 192°C

EXAMPLE 13:

2-butyl-1-[(4-(methoxycarbonyl)phenyl)methyl]-N-[(4-(N,N-dimethylamino)-phenyl)methyl]-N-[-1H-tetrazol-5-yl]-1H-imidazole-5-carboxamide
M PT. = 170°C

EXAMPLE 14:

2-butyl-1-[(4-(methoxycarbonyl)phenyl)methyl]-N-[(4-(phenylmethoxy)phenyl)-methyl]-N-[-1H-tetrazol-5-yl]-1H-imidazole-5-carboxamide
M PT. = 202°C

EXAMPLE 15:

2-butyl-1-[(4-(methoxycarbonyl)phenyl)methyl]-N-[(4-cyanophenyl)methyl]-N-[-1H-tetrazol-5-yl]-1H-imidazole-5-carboxamide
M PT. = 220°C

EXAMPLE 16:

2-butyl-1-[(4-(methoxycarbonyl)phenyl)methyl]-N-[(4-(1-methylethyl)phenyl)methyl]-N-[-1H-tetrazol-5-yl]-1H-imidazole-5-carboxamide
M PT. = 187°C

EXAMPLE 17:

2-butyl-1-[(4-(methoxycarbonyl)phenyl)methyl]-N-[biphenyl-4-yl-methyl]-N-[-1H-tetrazol-5-yl]-1H-imidazole-5-carboxamide
M PT. = 170°C

EXAMPLE 18:

2-butyl-1-[(4-(methoxycarbonyl)phenyl)methyl]-N-[(4-methoxycarbonyl)phenyl)-methyl]-N-[-1H-tetrazol-5-yl]-1H-imidazole-5-carboxamide
M PT. = 200°C

EXAMPLE 19:

2-butyl-1-[(4-(methoxycarbonyl)phenyl)methyl]-N-[(4-(trifluoromethyloxy)phenyl)-methyl]-N-[-1H-tetrazol-5-yl]-1H-imidazole-5-carboxamide
M PT. = 191°C

EXAMPLE 20:

2-butyl-1-[(4-(methoxycarbonyl)phenyl)methyl]-N-[(3,4-methylenedioxyphenyl)-methyl]-N-[-1H-tetrazol-5-yl]-1H-imidazole-5-carboxamide
M PT. = 210°C

EXAMPLE 21:

2-butyl-1-[(4-(ethoxycarbonyl)phenyl)methyl]-N-[(thien-2-yl)methyl]-N-[-1H-tetrazol-5-yl]-1H-imidazole-5-carboxamide
M PT. = 165°C

EXAMPLE 22:

2-butyl-1-[(4-(ethoxycarbonyl)phenyl)methyl]-N-[phenylmethyl]-N-[1H-tetrazol-5-yl]-1H-imidazole-5-carboxamide
M PT. = 184°C

EXAMPLE 23:

2-butyl-1-[(4-(pentyloxycarbonyl)phenyl)methyl]-N-[phenylmethyl]-N-[1H-tetrazol-5-yl]-1H-imidazole-5-carboxamide
M PT. = 181°C

EXAMPLE 24:

2-butyl-1-[(4-(pentyloxycarbonyl)phenyl)methyl]-N-[(4-chlorophenyl)methyl]-N-[1H-tetrazol-5-yl]-1H-imidazole-5-carboxamide
M PT. = 191°C

EXAMPLE 25:

2-butyl-1-[(4-(phenylmethoxycarbonyl)phenyl)methyl]-N-[(3,4-methylenedioxyphenyl)-methyl]-N-[1H-tetrazol-5-yl]-1H-imidazole-5-carboxamide
M PT. = 203°C

EXAMPLE 26:

2-butyl-1-[(4-(phenylmethoxycarbonyl)phenyl)methyl]-N-[(4-cyanophenyl)methyl]-N-[1H-tetrazol-5-yl]-1H-imidazole-5-carboxamide
M PT. = 133°C

EXAMPLE 27:

2-butyl-1-[(4-(1-(cyclohexyloxycarbonyloxy)ethyloxycarbonyl)phenyl)methyl]-N-[phenylmethyl]-N-[1H-tetrazol-5-yl]-1H-imidazole-5-carboxamide
M PT. = 130°C

EXAMPLE 28:

2-butyl-1-[(4-(1-(cyclohexyloxycarbonyloxy)ethyloxycarbonyl)phenyl)methyl]-N-[(4-chlorophenyl)methyl]-N-[1H-tetrazol-5-yl]-1H-imidazole-5-carboxamide
M PT. = 164°C

EXAMPLE 29:

2-butyl-1-[(4-(hydroxycarbonyl)phenyl)methyl]-N-[(thien-2-yl)methyl]-N-[1H-tetrazol-5-yl]-1H-imidazole-5-carboxamide.

To a suspension of 1.64 g (3.4×10^{-3} mole) of 2-butyl-1-[(4-(methoxycarbonyl)phenyl)methyl]-N-[(thien-2-yl)methyl]-N-[-1H-tetrazol-5-yl]-1H-imidazole-5-carboxamide, in 70 ml of methanol, is added 0.6 g (15×10^{-3} mole) of sodium hydroxide in solution in 6 ml of water, then this is heated to 60°C for two hours. The mixture is concentrated under reduced pressure, then the residue is solubilized in water. It is acidified by 1N hydrochloric acid until pH = 4.5. The solid obtained is filtered, washed in water and dried under vacuum in the presence of phosphoric anhydride. The raw product is recrystallized in methanol. 1.25 g in the form of white crystals is obtained (yield = 78%).

M PT. = 220°C

The following examples of products can be obtained by an operation similar to that of Example 29:

EXAMPLE 30:

1-[(4-(hydroxycarbonyl)phenyl)methyl]-2-propyl-N-[(thien-2-yl)methyl]-N-[-1H-tetrazol-5-yl]-1H-imidazole-5-carboxamide

M PT. = 243°C

EXAMPLE 31:

2-butyl-1-[(4-(hydroxycarbonyl)phenyl)methyl]-N-[phenylmethyl]-N-[1H-tetrazol-5-yl]-1H-imidazole-5-carboxamide

M PT. = 205°C

EXAMPLE 32:

2-butyl-1-[(4-(hydroxycarbonyl)phenyl)methyl]-N-[(furan-3-yl)methyl]-N-[1H-tetrazol-5-yl]-1H-imidazole-5-carboxamide

M PT. = 221°C

EXAMPLE 33:

2-butyl-1-[(4-(hydroxycarbonyl)phenyl)methyl]-N-[(4-methoxyphenyl)methyl]-N-[-1H-tetrazol-5-yl]-1H-imidazole-5-carboxamide
M PT. = 180 °C

EXAMPLE 34:

2-butyl-1-[(4-(hydroxycarbonyl)phenyl)methyl]-N-[(2-chlorophenyl)methyl]-N-[-1H-tetrazol-5-yl]-1H-imidazole-5-carboxamide
M PT. = 215 °C

EXAMPLE 35:

2-butyl-1-[(4-(hydroxycarbonyl)phenyl)methyl]-N-[(3-chlorophenyl)methyl]-N-[-1H-tetrazol-5-yl]-1H-imidazole-5-carboxamide
M PT. = 214 °C

EXAMPLE 36:

2-butyl-1-[(4-(hydroxycarbonyl)phenyl)methyl]-N-[(4-chlorophenyl)methyl]-N-[-1H-tetrazol-5-yl]-1H-imidazole-5-carboxamide
M PT. = 180 °C

EXAMPLE 37:

2-butyl-1-[(4-(hydroxycarbonyl)phenyl)methyl]-N-[(4-methylphenyl)methyl]-N-[-1H-tetrazol-5-yl]-1H-imidazole-5-carboxamide
M PT. = 184 °C

EXAMPLE 38:

2-butyl-1-[(4-(hydroxycarbonyl)phenyl)methyl]-N-[(napht-2-yl)methyl]-N-[-1H-tetrazol-5-yl]-1H-imidazole-5-carboxamide
M PT. = 222 °C

EXAMPLE 39:

2-butyl-1-[(4-(hydroxycarbonyl)phenyl)methyl]-N-[(3,4-dichlorophenyl)methyl]-N-[-1H-tetrazol-5-yl]-1H-imidazole-5-carboxamide
M PT. = 175°C

EXAMPLE 40:

2-butyl-1-[(4-(hydroxycarbonyl)phenyl)methyl]-N-[(4-trifluoromethyl-phenyl)methyl]-N-[-1H-tetrazol-5-yl]-1H-imidazole-5-carboxamide
M PT. = 215°C

EXAMPLE 41:

2-butyl-1-[(4-(hydroxycarbonyl)phenyl)methyl]-N-[(4-(N,N-dimethyl-amino)phenyl)methyl]-N-[-1H-tetrazol-5-yl]-1H-imidazole-5-carboxamide
M PT. = 190°C

EXAMPLE 42:

2-butyl-1-[(4-(hydroxycarbonyl)phenyl)methyl]-N-[(4-(phenylmethyloxy)phenyl)methyl]-N-[-1H-tetrazol-5-yl]-1H-imidazole-5-carboxamide
M PT. = 260°C

EXAMPLE 43:

2-butyl-1-[(4-(hydroxycarbonyl)phenyl)methyl]-N-[(4-(1-methylethyl)phenyl)methyl]-N-[-1H-tetrazol-5-yl]-1H-imidazole-5-carboxamide
M PT. = 244°C

EXAMPLE 44:

2-butyl-1-[(4-(hydroxycarbonyl)phenyl)methyl]-N-[biphenyl-4-yl-methyl]-N-[-1H-tetrazol-5-yl]-1H-imidazole-5-carboxamide
M PT. = 225°C

EXAMPLE 45:

2-butyl-1-[(4-(hydroxycarbonyl)phenyl)methyl]-N-[(4-hydroxycarbonylphenyl)methyl]-N-[-1H-tetrazol-5-yl]-1H-imidazole-5-carboxamide

M PT. = 267°C

EXAMPLE 46:

2-butyl-1-[(4-(hydroxycarbonyl)phenyl)methyl]-N-[(4-(trifluoromethyloxy)phenyl)methyl]-N-[-1H-tetrazol-5-yl]-1H-imidazole-5-carboxamide

M PT. = 204°C

EXAMPLE 47:

2-butyl-1-[(4-(hydroxycarbonyl)phenyl)methyl]-N-[(3,4-methylenedioxyphenyl)methyl]-N-[-1H-tetrazol-5-yl]-1H-imidazole-5-carboxamide

To a solution of 1.5 g (2.5×10^{-3} mole) of 2-butyl-1-[(4-(phenylmethoxycarbonyl)phenyl)methyl]-N-[(3,4-methylenedioxyphenyl)methyl]-N-[1H-tetrazol-5-yl]-1H-imidazole-5-carboxamide in 40 ml of dimethylformamide, is added under nitrogen atmosphere 0.15 g of 10% palladized charcoal. The suspension is then agitated under hydrogen atmosphere for 4 hours, under a pressure of 3.5×10^5 pascals. The catalyst is eliminated by filtration. Then water is added to the filtrate, then a 1N solution of sodium hydroxide is added to bring to alkaline pH. The aqueous phase is extracted with ethyl acetate and then is acidified with 1N hydrochloric acid until pH = 4. The precipitate product is filtered and washed in water. After recrystallization in isopropyl alcohol, 0.18 g of white crystals is obtained (yield = 14%).

M PT. = 166°C

The following example of a product can be obtained by an operation similar to that of Example 47:

EXAMPLE 48:

2-butyl-1-[(4-(hydroxycarbonyl)phenyl)methyl]-N-[(4-cyanophenyl)methyl]-N-[-1H-tetrazol-5-yl]-1H-imidazole-5-carboxamide

M PT. = 263°C

EXAMPLE 49:

2-butyl-1-[(4-(2-chlorophenylsulfonylaminocarbonyl)phenyl)methyl]-N-[(thien-2-yl)-methyl]-N-[-1H-tetrazol-5-yl]-1H-imidazole-5-carboxamide

0.63 g (1.35×10^{-3} mole) of 2-butyl-1-[(4-(hydroxycarbonyl)phenyl)methyl]-N-[(thien-2-yl)methyl]-N-[1H-tetrazol-5-yl]-1H-imidazole-5-carboxamide is suspended in 30 ml of dichloromethane. Then 0.5 g (4×10^{-3} mole) of 4-dimethylaminopyridine, 0.39 g (2×10^{-3} mole) of 2-chlorobenzenesulfonamide and 0.39 g of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride are added successively. The reaction medium is agitated at ambient temperature for 10 hours then the dichloromethane is evaporated under reduced pressure. The residue is taken up with water then acidified until pH = 3 with 1N hydrochloric acid. The precipitate is filtered, washed in water and ethanol. The precipitate is recrystallized in an ethanol-methanol mixture. 0.53 g of a white solid is obtained (yield = 61%).

M PT. = 250°C

EXAMPLE 50:

2-butyl-1-[(4-((1H-tetrazol-5-yl)aminocarbonyl)phenyl)methyl]-N-[phenylmethyl]-N-[1H-tetrazol-5-yl]-1H-imidazole-5-carboxamide

130 mg (0.8×10^{-3} mole) of 1-1'-carbonyldiimidazole is added to a solution of 320 mg (0.69×10^{-3} mole) of 2-butyl-1-[(4-(hydroxycarbonyl)phenyl)methyl]-N-[phenylmethyl]-N-[-1H-tetrazol-5-yl]-1H-imidazole-5-carboxamide, in 20 ml of tetrahydrofurane and 2 ml of dimethylformamide. The reaction mixture is brought to reflux for three hours then cooled to ambient temperature. Then 586 mg (0.69×10^{-3} mole) of 5-amino tetrazol is added. The reaction mixture is brought to reflux for

4 hours then left to return to ambient temperature for the night. The solvents are evaporated under reduced pressure, the residue is taken up with water than acidified to pH = 3 with 1N hydrochloric acid. The precipitate product is filtered, washed in water and dried. The product is recrystallized in methanol. 230 mg of white solid is obtained (yield = 64%).

M PT. = 202°C

In the following tables I to VI, a certain number of compounds according to the invention are collected. In the tables the symbols used have the following meanings:

n-Pr = $-CH_2-CH_2-CH_3$

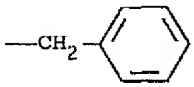
i-Pr = $-CH(CH_3)_2$

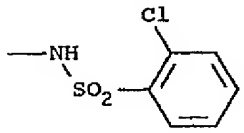
n-Bu = $-CH_2-CH_2-Ch_2-CH_3$

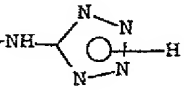
n-Pent = $-(CH_2)_4-CH_3$

DMA = $-N(CH_3)_2$

Ph = phenyl

Bn = 

OCSA = 

TA = 

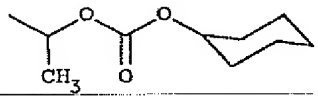
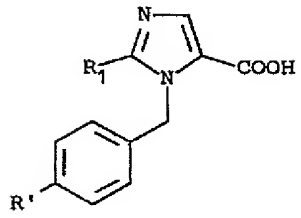
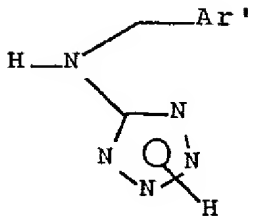
CHEC = 

Table I



PREPARATION	R_1	R'	M PT. (°C)
2	n-Bu	CO_2CH_3	212
3	n-Bu	$CO_2C_2H_5$	202
4	n-Bu	CO_2-n-Pent	168
5	n-Bu	CO_2-Bn	170
6	n-Bu	CO_2-CHEC	50
7	n-Pr	CO_2CH_3	225

Table II



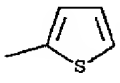
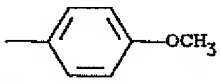
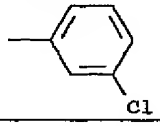
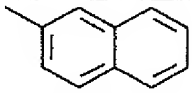
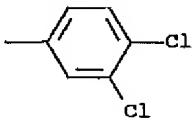
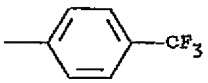
PREPARATION	Ar'	M PT. (°C)
8		210
9		186
10		230
11		208
12		234
13		220
14		226

Table II (continued)

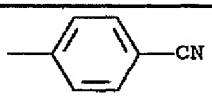
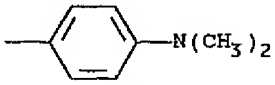
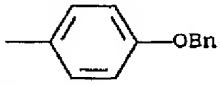
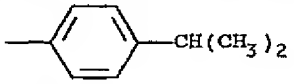
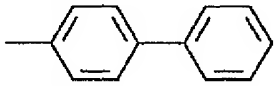
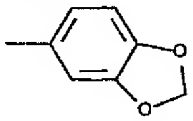
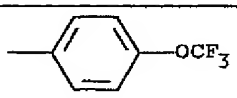
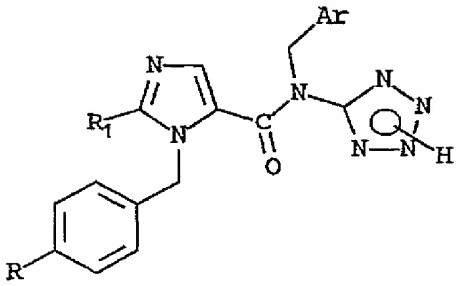
PREPARATION	Ar'	M PT. (°C)
15		230
16		213
17		223
18		205
19		260
20		220
21		224

Table III



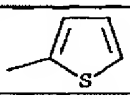
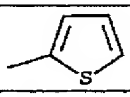
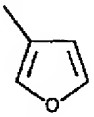
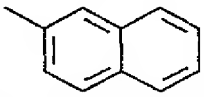
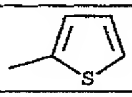
EXAMPLE	R_1	R	Ar	M PT. (°C)
1	n-Bu	CO_2CH_3		190
2	n-Pr	CO_2CH_3		191
4	n-Bu	CO_2CH_3		200
10	n-Bu	CO_2CH_3		206
21	n-Bu	$CO_2C_2H_5$		165
22	n-Bu	$CO_2C_2H_5$	Ph	184

Table III (continued)

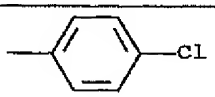
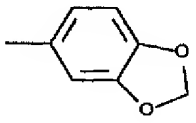
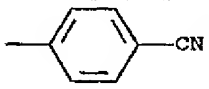
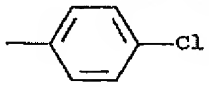
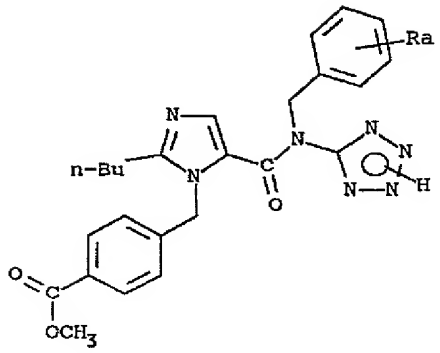
EXAMPLE	R_1	R	Ar	M PT. (°C)
23	n-Bu	CO_2-n-Pent	Ph	181
24	n-Bu	CO_2-n-Pent		191
25	n-Bu	CO_2-Bn		203
26	n-Bu	CO_2-Bn		133
27	n-Bu	CO_2-CHEC	Ph	130
28	n-Bu	CO_2-CHEC		164

Table IV

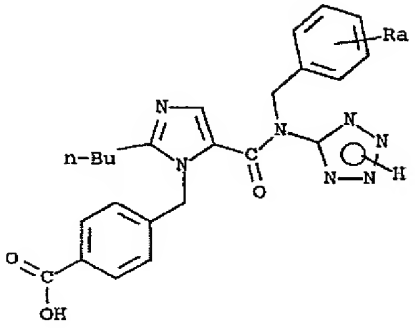


EXAMPLE	Ra	M PT. (°C)
3	H	190
5	4-OCH_3	209
6	2-Cl	151
7	3-Cl	192
8	4-Cl	204
9	4-CH_3	194
11	3,4-diCl	213
12	4-CF_3	192
13	4-DMA	170

TABLE IV (continued)

EXAMPLE	Ra	M PT. (°C)
14	4-O-Bn	202
15	4-CN	220
16	4-i-Pr	187
17	4-Ph	170
18	4-CO_2CH_3	200
19	4-OCF_3	191
20	3,4-(O-CH_2-O)	210

Table V

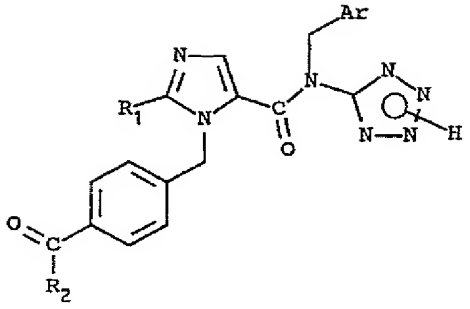


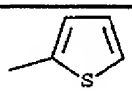
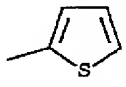
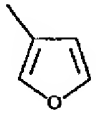
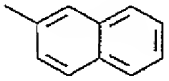
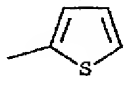
EXAMPLE	Ra	M PT. (°C)
31	H	205
33	4-OCH_3	180
34	2-Cl	215
35	3-Cl	214
36	4-Cl	180
37	4-CH_3	184
39	3,4-diCl	175
40	4-CF_3	215
41	4-DMA	190
42	4-O-Bn	260

TABLE V (continued)

EXAMPLE	Ra	M PT. (°C)
43	4-i-Pr	244
44	4-Ph	225
45	4-CO_2H	267
46	4-O-CF_3	204
47	3.4-(O-CH_2-O)	166
48	4-CN	263

Table VI



EXAMPLE	R_1	Ar	R_2	M PT. (°C)
29	n-Bu		OH	220
30	n-Pr		OH	243
32	n-Bu		OH	221
38	n-Bu		OH	222
49	n-Bu		OCSA	250
50	n-Bu	Ph	TA	202

The products according to the invention are inhibitors of the effects of angiotensin II.

The activity of the compounds according to the invention as antagonists of the angiotensin II vascular receptor was evaluated by their efficacy to antagonize the contractile response induced by angiotensin II in rabbit isolated aortic rings. The rings are suspended in a Krebs-Henseleit bath maintained at 37°C and aerated by an O_2/CO_2 mixture (95/5, V/V), then stretched at a resting tension of 2 g. After one hour of rest, a contraction is caused by angiotensin II (3×10^{-9}) in the presence of the product to be tested that was preincubated for 15 minutes. The concentration (expressed in nanomoles) of the product to be tested producing an inhibition of 50% of the contractile response (IC_{50}) is calculated from the concentration-response curve. The results obtained with a certain number of compounds according to the invention are collected in Table VII.

The compounds according to the invention have been tested on conscious normotensive rats for their propensity to inhibit a pressor response induced by angiotensin II. The compounds according to the invention were administered orally at a dose of 3 mg/kg. The results are expressed in maximum inhibition % of the pressor response to angiotensin II (Table VIII).

By way of comparison, pharmacological activity tests were also done with a known reference product presented as being a preferred angiotensin II inhibitor in patent application EP-A-425 211, and referred to as "Z" in the following tables, this Z product having the formula:

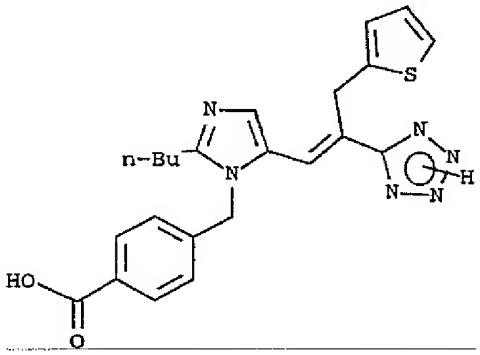


Table VII

EXAMPLE	IC_{50} ($x10^{-9}$ M)
29	1.7
31	2.2
32	2.0
33	0.5
34	3.2
35	1.6
36	0.4
37	1.7
38	5.2
39	1.0
41	4.6
49	2.7
50	2.1
Z	6.2

Table VIII

EXAMPLE	Inhibition %
1	47.9
3	54.7
29	61.8
31	72.7
Z	22.0

Reading the pharmacological test results in Tables VII and VIII shows that the products according to the invention have an angiotensin II effect inhibitory activity that is definitely higher than reference product Z.

The products according to the invention are useful in therapeutics in the treatment or prevention of high blood pressure, glaucoma, circulatory disorders, restenosis following angioplasties, the development of atheromatous or fibroproliferative lesions, diabetic nephropathy and retinopathy, infarct and angina and to improve cognitive function.

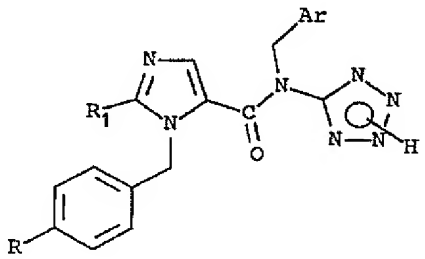
According to the invention, a therapeutic composition characterized in that the composition contains at least one compound of formula I or one of its addition salts in a therapeutically effective quantity in combination with a physiologically acceptable excipient is recommended.

The use of compounds of formula I or their addition salts as angiotensin II antagonist agents to obtain a preventive or curative medication for high blood pressure, circulatory disorders or glaucoma is also recommended.

CLAIMS

1. An imidazole-5-carboxamide compound, characterized in that the compound is chosen from the group comprised of:

(i) N-(tetrazol-5-yl)-imidazole-5-carboxamide derivatives of formula:



(I)

in which:

- R_1 represents an n-propyl or n-butyl group,
- R represents:
  * a CO_2R_2 group in which R_2 represents:
    - the hydrogen atom,
    - a C_1-C_5 linear or branched alkyl group,
    - a benzyl group,
    - a group of formula $-CH_3$-O-CO-R_4 in which R_3 represents a hydrogen atom or a methyl group and R_4 represents a C_1-C_5 linear or branched alkyl group, a C_2-C_6 linear or branched alkoxy group, or a C_5-C_6 cycloalkyloxy group,
  * a 2-chloro-phenyl-sulfonylamino-carbonyl group, or
  * a tetrazol-5-yl-amino-carbonyl group,
- Ar represents:
  * a phenyl group optionally substituted by one or more of the following atoms or groups: methyl, 1-methyl-ethyl, phenyl, chloro, cyano, methoxy, benzyloxy, trifluoromethyloxy, trifluoromethyl, N,N-dimethyl-amino, carboxyl, methoxycarbonyl,
  * a 3,4-methylenedioxy-phenyl group,
  * a 3-furanyl group,
  * a 2-thienyl group, or

* a 2-naphtyl group; and

(ii) their addition salts with mineral or organic bases

2. The compound according to Claim 1 characterized in that

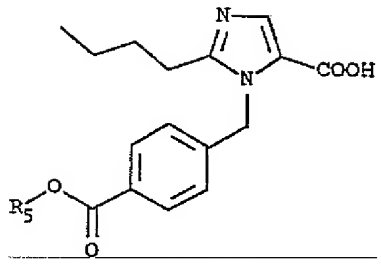
- R_1 represents an n-butyl group,
- R and Ar respectively represent the following pairs:
  * Carboxyl and 2-thienyl,
  * Carboxyl and phenyl,
  * Carboxyl and 3-furanyl,
  * Carboxyl and 4-chloro-phenyl,
  * Carboxyl and 3,4-dichloro-phenyl,
  * Carboxyl and 3-chloro-phenyl,
  * Carboxyl and 4-methyl-phenyl,
  * Carboxyl and 3,4-methylenedioxyphenyl, or
  * 1-(cyclohexyloxycarbonyloxy)-ethyloxycarbonyl and phenyl.

3. The compound according to Claim 2 characterized in that the compound is salified by an organic or mineral base.

4. A therapeutic composition characterized in that the composition contains at least one compound of formula I or one of its addition salts in a therapeutically effective quantity, in combination with a physiologically acceptable excipient.

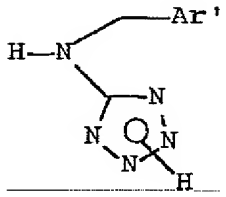
5. The use of a compound of formula I as an angiotensin II antagonist agent to obtain a preventive or curative medication for high blood pressure, circulatory disorders and glaucoma.

6. An intermediate compound, useful in the synthesis of a compound according to Claim 1, characterized in that the intermediate compound is an imidazole-5-carboxylic acid of formula:



in which R_5 represents an ethyl group, an n-pentyl group, a benzyl group or a group of formula CHR_3-O-COR_4 in which R_3 represents a hydrogen atom or a methyl group and R_4 represents a C_1-C_5 linear or branched alkyl group, a C_2-C_6 linear or branched alkoxy group or a C_5-C_6 cycloalkyloxy group.

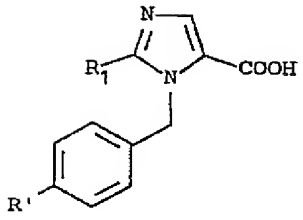
7. An intermediate compound, useful in the synthesis of a compound according to Claim 1, characterized in that the intermediate compound is a tetrazol-5-amine of formula:



in which Ar' represents a 2-thienyl group, a 2-furanyl group or a phenyl group substituted by one of the following groups: 4-methoxy, 4-trifluoromethyl, 4-cyano, 4-dimethylamino, 4-benzyloxy, 4-(1-methylethyl); 4-phenyl, 3,4-methylenedioxy, 4-trifluoromethyloxy, 3,4-dichloro.

8. A process of preparation of a compound according to Claim 1 characterized in that:

a) one cause to react a compound of formula

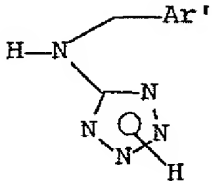


(II)

in which

- R_1 represents an n-propyl or n-butyl group,
- R' represents a $CO_2R'_2$ group in which R'_2 represents
  - a C_1-C_5 linear or branched alkyl group,
  - a benzyl group, or
  - a group of formula $-CHR_3-O-CO-R_4$ in which R_3 represents a hydrogen atom or a methyl group and R_4 represents a C_1-C_5 linear or branched alkyl group, a C_2-C_6 linear or branched alkoxy group, or a C_5-C_6 cycloalkyloxy group,

with a compound of formula:



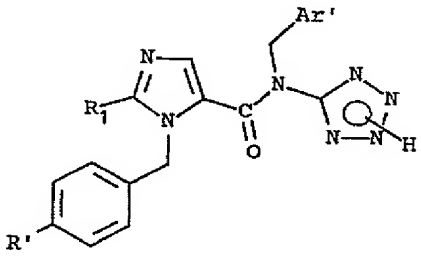
(III)

in which Ar' represents:

* a phenyl group optionally substituted by one or more of the following groups or atoms: methyl, 1-methyl-ethyl, phenyl, chloro, cyano, methoxy, benzyloxy, trifluoromethyloxy, trifluoromethyl, N,N-dimethylamino or methoxycarbonyl,
* a 3,4-(methylenedioxy)phenyl group,
* a 3-furanyl group,
* a 2-thienyl group, or
* a 2-naphtyl group,

to form an amide bond, in an organic solvent and in the presence of a catalyst, at a temperature

between ambient temperature and the reflux temperature of the reaction medium, under atmospheric pressure, for 0.5 to 24 hours, and to obtain a compound of formula:



(I')

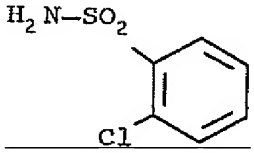
in which R_1, R' and Ar' have the same meanings as above; and,

b) if necessary, the compounds of formula I' thus obtained are subjected to the following treatments:

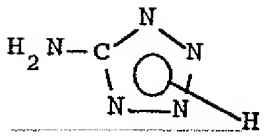
(i) a compound of formula I' is saponified, in which at least one of the R' and Ar' groups represents or contains an alkoxycarbonyl group, in the presence of a strong base in dimethoxyethane or an alcohol to obtain a compound of formula I in which at least one of the R and Ar groups represents or contains a COOH group, or

(ii) a compound of formula I' is deprotected, in which R' represents a benzyloxycarbonyl group in the presence of a catalyst to obtain a compound of formula I in which R represents a COOH group, then

(iii) one acylates an arylsulfonamide of formula:



or one acylates the 5-amino-tetrazol of formula:



by a monoacid of formula I obtained in the previous step (i) or (ii), in which R represents a COOH group and Ar has the same meanings as above for Ar' in formula III, to obtain a compound of formula I in which R_1 and Ar have the same meanings as above and R represents a 2-chlorophenylsulfonylaminocarbonyl group or a (tetrazol-5-yl)-aminocarbonyl group.

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PRELIMINARY SEARCH REPORT

Established on the basis of the last claims filed before start of search

FA 488755
FR 9308767

DOCUMENTS CONSIDERED TO BE RELEVANT		Relevant to claim of the examined application	
Category	Citation of the document with indication, if needed, of the relevant parties		
A	CHEMICAL ABSTRACTS, Vol. 118, No. 21, 24 May 1993, Columbus, Ohio, U.S.; abstract No. 213064r, GIICHI GOTO ET AL "Preparation of five-membered heterocyclic amide derivatives" page 918; *abstract* & JP-A-04 247 081 (TAKEDA CHEMICAL INDUSTRIES) ---	1,4,5	
A	FR-A-1 585 857 (JANSSEN PHARMACEUTICA) *page 1, left column; claim 1* ---	1,4,5	
			TECHNICAL FIELDS SEARCHED (Int.Cl.5)
A	CHEMICAL ABSTRACTS, Vol. 111, No. 1, 3 July 1989, Columbus, Ohio, U.S.; abstract No. 6655z, H.P. BENECKE ET AL "Synthesis hydrolytic refractivity and initial bioevaluation of (R)-etomidate analogs. Part. Synthesis and hydrolytic refractivity of (R)-etomidate analogs" page 641; *abstract* & REPORT (CRDEC-CR-88016; ORDER NO. AD-A190763) (49 PP) 1987 compound of CN (RN): 118664-80-5 ---	1,4,5	C07D A61K
A	JOURNAL OF THE CHEMICAL SOCIETY (C). No. 4, 1971 LETCHWORTH GB pages 703-706 F. L. SCOTT ET AL "Preparation and spectra of aminotetrazoles benzylated in the nucleus or in the side-chain" *page 704* -----	7	

Date of completion of the search	Examiner
17 March 1994	Voyiazoglou, D

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